nature COMMUNICATIONS

ARTICLE

Received 12 Mar 2015 | Accepted 27 Oct 2015 | Published 21 Jan 2016

DOI: 10.1038/ncomms10023 OPEN

# Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function

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Reduced glomerular filtration rate defines chronic kidney disease and is associated with cardiovascular and all-cause mortality. We conducted a meta-analysis of genome-wide association studies for estimated glomerular filtration rate (eGFR), combining data across 133,413 individuals with replication in up to 42,166 individuals. We identify 24 new and confirm 29 previously identified loci. Of these 53 loci, 19 associate with eGFR among individuals with diabetes. Using bioinformatics, we show that identified genes at eGFR loci are enriched for expression in kidney tissues and in pathways relevant for kidney development and transmembrane transporter activity, kidney structure, and regulation of glucose metabolism. Chromatin state mapping and DNase I hypersensitivity analyses across adult tissues demonstrate preferential mapping of associated variants to regulatory regions in kidney but not extra-renal tissues. These findings suggest that genetic determinants of eGFR are mediated largely through direct effects within the kidney and highlight important cell types and biological pathways.

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Chronic kidney disease (CKD) is a global public health problem[1–3], and is associated with an increased risk for cardiovascular disease, all-cause mortality and end-stage renal disease[4,5]. Few new therapies have been developed to prevent or treat CKD over the past two decades[1,6], underscoring the need to identify and understand the underlying mechanisms of CKD.

Prior genome-wide association studies (GWAS) have identified multiple genetic loci associated with CKD and estimated glomerular filtration rate (eGFR), a measure of the kidney's filtration ability that is used to diagnose and stage CKD[7–15]. Subsequent functional investigations point towards clinically relevant novel mechanisms in CKD that were derived from initial GWAS findings[16], providing proof of principle that locus discovery through large-scale GWAS efforts can translate to new insights into CKD pathogenesis.

To identify additional genetic variants associated with eGFR and guide future experimental studies of CKD-related mechanisms, we have now performed GWAS meta-analyses in up to 133,413 individuals, more than double the sample size of previous studies. Here we describe multiple novel genomic loci associated with kidney function traits and provide extensive locus characterization and bioinformatics analyses, further delineating the physiologic basis of kidney function.

## Results

**Stage 1 discovery analysis**. We analysed associations of eGFR based on serum creatinine (eGFRcrea), cystatin C (eGFRcys, an additional, complementary biomarker of renal function) and CKD (defined as eGFRcrea $<60\,ml\,min^{-1}$ per $1.73\,m^2$) with $\sim$2.5 million autosomal single-nucleotide polymorphisms (SNPs) in up to 133,413 individuals of European ancestry from 49 predominantly population-based studies (Supplementary Table 1). Results from discovery GWAS meta-analysis are publicly available at http://fox.nhlbi.nih.gov/CKDGen/. We performed analyses in each study sample in the overall population and stratified by diabetes status, since genetic susceptibility to CKD may differ in the presence of this strong clinical CKD risk factor. Population stratification did not impact our results as evidenced by low genomic inflation factors in our meta-analyses, which ranged from 1.00 to 1.04 across all our analyses (Supplementary Fig. 1).

In addition to confirming 29 previously identified loci[7–9] (Fig. 1a; Supplementary Table 2), we identified 48 independent novel loci (Supplementary Table 3) where the index SNP, defined as the variant with the lowest $P$ value in the region, had an association $P$ value $<1.0\times10^{-6}$. Of these 48 novel SNPs, 21 were genome-wide significant with $P$ values $<5.0\times10^{-8}$. Overall, 43 SNPs were identified in association with eGFRcrea (nine in the non-diabetes sample), one with eGFRcys and four with CKD, as reported in Supplementary Table 3. Manhattan plots for CKD, eGFRcys and eGFRcrea in diabetes are shown in Fig. 1b,c and Supplementary Fig. 2, respectively.

**Stage-2 replication**. Novel loci were tested for replication in up to 42,166 additional European ancestry individuals from 15 studies (Supplementary Table 1). Of the 48 novel candidate SNPs submitted to replication, 24 SNPs demonstrated a genome-wide significant combined stage 1 and 2 $P$ value $<5.0\times10^{-8}$ (Table 1). Of these, 23 fulfilled additional replication criteria ($q$-value $<0.05$ in stage 2). Only rs6795744 at the *WNT7A* locus demonstrated suggestive replication ($P$ value $<5.0\times10^{-8}$, $q$-value $>0.05$). Because serum creatinine is used to estimate eGFRcrea, associated genetic loci may be relevant to creatinine production or metabolism rather than kidney function *per se*. For this reason, we contrasted associations of eGFRcrea versus eGFRcys, the latter estimated from an alternative and creatinine-independent biomarker of GFR (Supplementary Fig. 3; Supplementary Table 4). The majority of loci (22/24) demonstrated consistent effect directions of their association with both eGFRcrea and eGFRcys.

Association plots of the 24 newly identified genomic regions that contain a replicated or suggestive index SNP appear in Supplementary Fig. 4. The odds ratio for CKD for each of the novel loci ranged from 0.93 to 1.06 (Supplementary Table 4). As evidenced by the relatively small effect sizes, the proportion of phenotypic variance of eGFRcrea explained by all new and known loci was 3.22%: 0.81% for the newly uncovered loci and 2.41% for the already known loci.

**Associations stratified by diabetes and hypertension status**. The effects of the 53 known and novel loci in individuals with (stage 1 + stage 2 $n=16{,}477$) and without (stage 1 + stage 2 $n=154{,}881$) diabetes were highly correlated (correlation coefficient: 0.80; 95% confidence interval: 0.67, 0.88; Supplementary Fig. 5) and of similar magnitude (Fig. 2; Supplementary Table 5), suggesting that identification of genetic loci in the overall population may also provide insights into loci with potential importance among individuals with diabetes. The previously identified *UMOD* locus showed genome-wide significant association with eGFRcrea among those with diabetes (Supplementary Fig. 2; rs12917707, $P$ value $=2.5\times10^{-8}$), and six loci (*NFKB1*, *UNCX, TSPAN9, AP5B1, SIPA1L3* and *PTPRO*) had nominally significant associations with eGFRcrea among those with diabetes. Of the previously identified loci, 13 demonstrated nominal associations among those with diabetes, for a total of 19 loci associated with eGFRcrea in diabetes.

Exploratory comparison of the association effect sizes in subjects with and without hypertension based on our previous work[7] showed that novel and known loci are also similarly associated with eGFRcrea among individuals with and without hypertension (Supplementary Fig. 6).

**Tests for SNP associations with related phenotypes**. We tested for overlap with traits that are known to be associated with kidney function in the epidemiologic literature by investigating SNP associations with systolic and diastolic blood pressure[17], myocardial infarction[18], left ventricular mass[19], heart failure[20], fasting glucose[21] and urinary albumin excretion (CKDGen Consortium, personal communication). We observed little association of the 24 novel SNPs with other kidney function-related traits, with only 2 out of 165 tests reaching the Bonferroni significance level of 0.0003 (see Methods and Supplementary Table 6).

To investigate whether additional traits are associated with the 24 new eGFR loci, we queried the NHGRI GWAS catalog (www.genome.gov). Overall, nine loci were previously identified in association with other traits at a $P$ value of $5.0\times10^{-8}$ or lower (Supplementary Table 7), including body mass index (*ETV5*) and serum urate (*INHBC*, *A1CF* and *AP5B1*).

**Trans-ethnic analyses**. To assess the generalizability of our findings across ethnicities, we evaluated the association of the 24 newly identified loci with eGFRcrea in 16,840 participants of 12 African ancestry population studies (Supplementary Table 8) and in up to 42,296 Asians from the AGEN consortium[11] (Supplementary Table 9). Seven SNPs achieved nominal direction-consistent significance ($P<0.05$) in AGEN, and one SNP was significant in the African ancestry meta-analysis (Supplementary Table 9). Random-effect meta-analysis showed that 12 loci (*SDCCAG8*, *LRP2*, *IGFBP5*, *SKIL*, *UNCX*, *KBTBD2*, *A1CF*, *KCNQ1*, *AP5B1*, *PTPRO*, *TP53INP2* and *BCAS1*) had fully consistent effect direction across the three ethnic groups

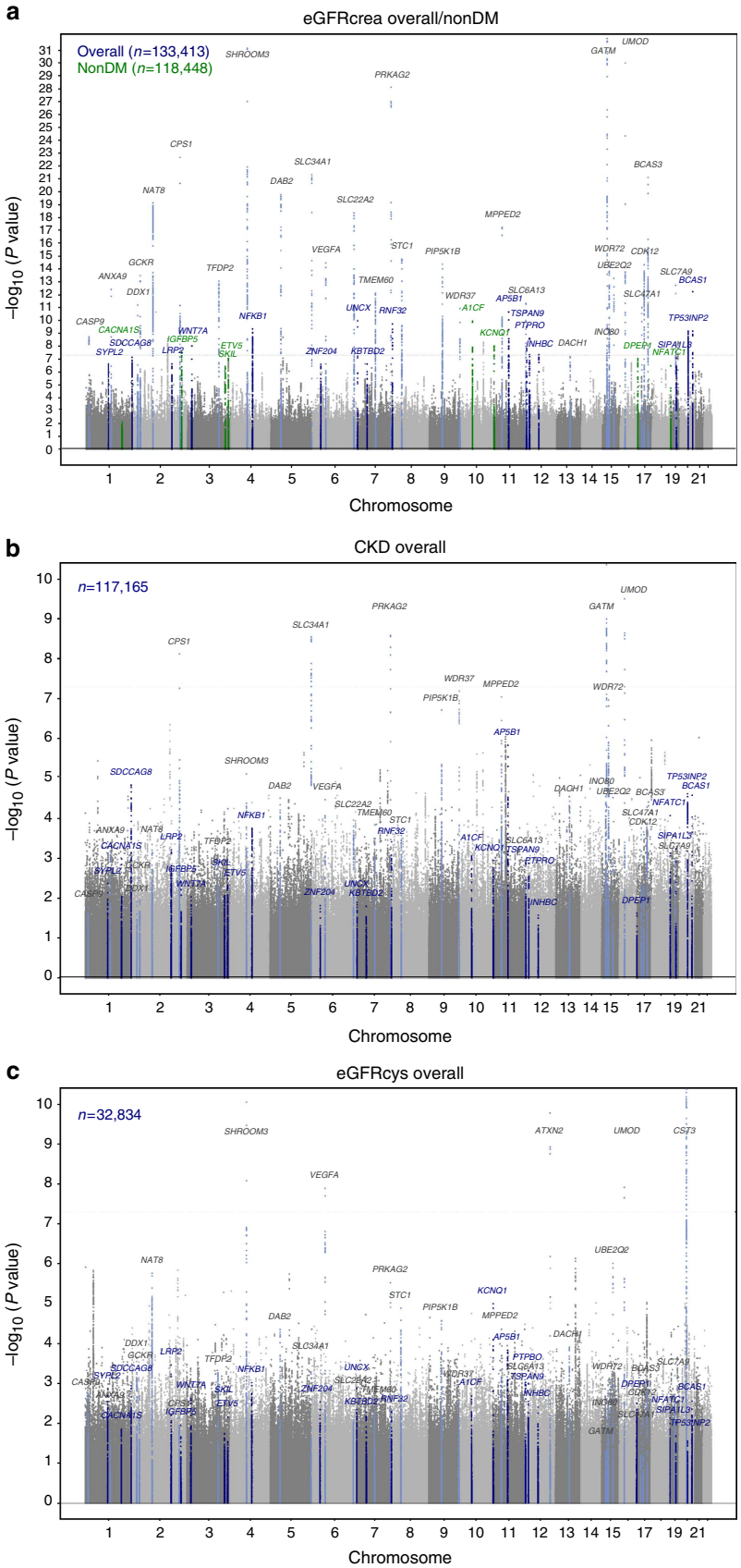


**Figure 1 | Discovery stage genome-wide association analysis.** Manhattan plots for eGFRcrea, CKD and eGFRcys. Previously reported loci are highlighted in light blue (grey labels). (**a**) Novel loci uncovered for eGFRcrea in the overall and in the non-diabetes groups are highlighted in blue and green, respectively. (**b**) Results from CKD analysis with highlighted known and novel loci for eGFRcrea. (**c**) Results from eGFRcys with highlighted known and novel loci for eGFRcrea and known eGFRcys loci.

**Table 1 | The 24 novel SNPs associated with eGFRcrea in European ancestry individuals.**

| SNP ID* | Chr. | Position (bp)† | Locus name‡ | Effect/Non effect allele (EAF) | SNP function§ | Stage 1 (discovery)‖ | | Stage 2 (replication) | | Combined analysis¶ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Beta | *P* value | Beta | *q*-value | Beta | *P* value# | $I^2$ %** |
| *The eight loci whose smallest P value was observed in the 'no diabetes' group* | | | | | | | | | | | | |
| rs3850625 | 1 | 201,016,296 | *CACNA1S* | A/G (0.12) | Exonic, nonsyn. SNV | 0.0080 | 2.55E − 09 | 0.0071 | 5.46E − 03 | 0.0083 | 6.82E − 11 | 0 |
| rs2712184 | 2 | 217,682,779 | *IGFBP5* | A/C (0.58) | Intergenic | − 0.0049 | 1.65E − 08 | − 0.0055 | 2.06E − 03 | − 0.0053 | 1.33E − 10 | 0 |
| rs9682041 | 3 | 170,091,902 | *SKIL* | T/C (0.87) | Intronic | − 0.0067 | 1.36E − 07 | − 0.0046 | 2.33E − 02 | − 0.0068 | 2.58E − 08 | 2 |
| rs10513801 | 3 | 185,822,353 | *ETV5* | T/G (0.87) | Intronic | 0.0070 | 3.80E − 09 | 0.0046 | 1.79E − 02 | 0.0072 | 1.03E − 09 | 0 |
| rs10994860 | 10 | 52,645,424 | *A1CF* | T/C (0.19) | UTR5 | 0.0075 | 1.00E − 11 | 0.0061 | 5.46E − 03 | 0.0077 | 1.07E − 12 | 2 |
| rs163160 | 11 | 2,789,955 | *KCNQ1* | A/G (0.82) | Intronic | 0.0067 | 9.02E − 09 | 0.0050 | 9.89E − 03 | 0.0065 | 2.26E − 09 | 14 |
| rs164748 | 16 | 89,708,292 | *DPEP1* | C/G (0.53) | Intergenic | 0.0047 | 9.92E − 09 | 0.0019 | 4.19E − 02 | 0.0046 | 1.95E − 08 | 17 |
| rs8091180 | 18 | 77,164,243 | *NFATC1* | A/G (0.56) | Intronic | − 0.0054 | 1.43E − 08 | − 0.0052 | 5.46E − 03 | − 0.0060 | 1.28E − 09 | 0 |
| *The 16 loci whose smallest P value was observed in the 'overall' group* | | | | | | | | | | | | |
| rs12136063 | 1 | 110,014,170 | *SYPL2* | A/G (0.70) | Intronic | 0.0049 | 2.33E − 07 | 0.0028 | 2.31E − 02 | 0.0045 | 4.71E − 08 | 0 |
| rs2802729 | 1 | 243,501,763 | *SDCCAG8* | A/C (0.43) | Intronic | − 0.0050 | 7.37E − 08 | − 0.0029 | 2.05E − 02 | − 0.0046 | 2.20E − 08 | 9 |
| rs4667594 | 2 | 170,008,506 | *LRP2* | A/T (0.53) | Intronic | − 0.0045 | 2.37E − 07 | − 0.0043 | 5.62E − 03 | − 0.0044 | 3.52E − 08 | 4 |
| rs6795744†† | 3 | 13,906,850 | *WNT7A* | A/G (0.15) | Intronic | 0.0071 | 9.60E − 09 | 0.0019 | 5.15E − 02 | 0.0060 | 3.33E − 08 | 18 |
| rs228611 | 4 | 103,561,709 | *NFKB1* | A/G (0.47) | Intronic | − 0.0055 | 4.66E − 10 | − 0.0060 | 8.91E − 04 | − 0.0056 | 3.58E − 12 | 3 |
| rs7759001 | 6 | 27,341,409 | *ZNF204* | A/G (0.76) | ncRNA intronic | − 0.0053 | 2.64E − 07 | − 0.0045 | 9.10E − 03 | − 0.0051 | 1.75E − 08 | 0 |
| rs10277115 | 7 | 1,285,195 | *UNCX* | A/T (0.23) | Intergenic | 0.0095 | 1.05E − 10 | 0.0079 | 9.03E − 04 | 0.0090 | 8.72E − 14 | 0 |
| rs3750082 | 7 | 32,919,927 | *KBTBD2* | A/T (0.33) | Intronic | 0.0049 | 2.52E − 07 | 0.0031 | 1.96E − 02 | 0.0045 | 3.22E − 08 | 2 |
| rs6459680 | 7 | 156,258,568 | *RNF32* | T/G (0.74) | Intergenic | − 0.0065 | 1.96E − 10 | − 0.0019 | 4.62E − 02 | − 0.0055 | 1.07E − 09 | 0 |
| rs4014195 | 11 | 65,506,822 | *AP5B1* | C/G (0.64) | Intergenic | 0.0061 | 2.19E − 11 | 0.0034 | 1.42E − 02 | 0.0055 | 1.10E − 11 | 0 |
| rs10491967 | 12 | 3,368,093 | *TSPAN9* | A/G (0.10) | Intronic | − 0.0092 | 3.03E − 10 | − 0.0106 | 3.93E − 04 | − 0.0095 | 5.18E − 14 | 0 |
| rs7956634 | 12 | 15,321,194 | *PTPRO* | T/C (0.81) | Intronic | − 0.0068 | 2.46E − 09 | − 0.0069 | 1.51E − 03 | − 0.0068 | 7.17E − 12 | 0 |
| rs1106766 | 12 | 57,809,456 | *INHBC* | T/C (0.22) | Intergenic | 0.0062 | 4.67E − 08 | 0.0058 | 8.79E − 03 | 0.0061 | 2.41E − 09 | 9 |
| rs11666497 | 19 | 38,464,262 | *SIPA1L3* | T/C (0.18) | Intronic | − 0.0064 | 8.58E − 08 | − 0.0041 | 1.53E − 02 | − 0.0058 | 4.25E − 08 | 24 |
| rs6088580 | 20 | 33,285,053 | *TPS3INP2* | C/G (0.47) | Intergenic | − 0.0055 | 7.17E − 10 | − 0.0027 | 2.31E − 02 | − 0.0049 | 1.79E − 09 | 0 |
| rs17216707 | 20 | 52,732,362 | *BCAS1* | T/C (0.79) | Intergenic | − 0.0084 | 5.96E − 13 | − 0.0051 | 6.69E − 03 | − 0.0077 | 8.83E − 15 | 1 |

bp, basepairs; Chr, chromosome; EAF, effect allele frequency; eGFRcrea, eGFR based on serum creatinine; GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism; UTR, untranslated region.
*SNPs are grouped by the stratum where the smallest *P* value in the discovery and combined analysis was observed. In the 'no diabetes' group, sample size/number of studies were equal to 118,448/45, 36,433/13 and 154,881/58, in the discovery, replication and combined analyses, respectively. In the 'overall' group, the numbers for the three analyses were equal to 133,413/48, 42,116/14 and 175,579/62, respectively.
†On the basis of RefSeq genes (build 37).
‡Conventional locus name based on relevant genes in the region as identified by bioinformatic investigation (Supplementary Table 12) or closest gene. A complete overview of the genes in each locus is given in the regional association plots (Supplementary Fig. 4).
§SNP function is derived from NCBI RefSeq genes and may not correspond to the named gene.
‖Twice genomic-control (GC) corrected *P* value from discovery GWAS meta-analysis: at the individual study level and after the meta-analysis.
¶For random-effect estimate, see Supplementary Table 4.
#*P* value of the meta-analysis of the twice GC-corrected discovery meta-analysis results and replication studies.
**Between-study heterogeneity, as assessed by the $I^2$. Q statistic *P* value >0.05 for all SNPs, except rs11666497 (*SIPA1L3*, *P* value = 0.04).
††For this SNP, the conditions for replication were not all met (*q*-value >0.05 in the replication stage).

(Supplementary Fig. 7), suggesting that our findings can likely be generalized beyond the European ancestry group.

To identify additional potentially associated variants and more formally evaluate trans-ethnic heterogeneity of the loci identified through meta-analysis in European ancestry populations, we performed a trans-ethnic meta-analysis[22], combining the 12 African ancestry studies with the 48 European Ancestry studies used in the discovery analysis of eGFRcrea. Of the 24 new loci uncovered for eGFRcrea, 15 were also genome-wide significant in the trans-ethnic meta-analysis (defined as $\log_{10}$ Bayes Factor >6, Supplementary Table 10), indicating that for most of these loci, there is little to no allelic effect heterogeneity across the two ethnic groups. No additional loci were significantly associated with $\log_{10}$ Bayes Factor >6.

**Bioinformatic and functional characterization of new loci**. We used several techniques to prioritize and characterize genes underlying the identified associations, uncover connections between associated regions, detect relevant tissues and assign functional annotations to associated variants. These included expression quantitative trait loci (eQTL) analyses, pathway analyses, DNAse I hypersensitivity site (DHS) mapping, chromatin mapping, manual curation of genes in each region and zebrafish knockdown.

**eQTL analysis**. We performed eQTL analysis using publically available eQTL databases (see Methods). These analyses connected novel SNPs to transcript abundance of *SYPL2*, *SDCCAG8*, *MANBA*, *KBTBD2*, *PTPRO* and *SPATA33* (*C16orf55*), thereby supporting these as potential candidate genes in the respective associated regions (Supplementary Table 11).

**Pathway analyses**. We used a novel method, Data-driven Expression Prioritized Integration for Complex Traits (DEPICT)[23], to prioritize genes at associated loci, to test whether genes at associated loci are highly expressed in specific tissues or cell types and to test whether specific biological pathways and gene sets are enriched for genes in associated loci. On the basis of all SNPs with eGFRcrea association *P* values $<10^{-5}$ in the discovery meta-analysis, representing 124 independent regions, we identified at least one significantly prioritized gene in 49 regions, including in 9 of the 24 novel genome-wide significant regions (Supplementary Table 12). Five tissue and cell type annotations were enriched for expression of genes from the associated regions, including the kidney and urinary tract, as well as hepatocytes and adrenal glands and cortex (Fig. 3a; Supplementary Table 13). Nineteen reconstituted gene sets showed enrichment of genes mapping into the associated regions at a permutation *P* value $<10^{-5}$ (Supplementary Table 14; Fig. 4), highlighting processes related to renal development, kidney transmembrane transporter activity, kidney and urogenital system morphology, regulation of glucose metabolism, as well as specific protein complexes important in renal development.

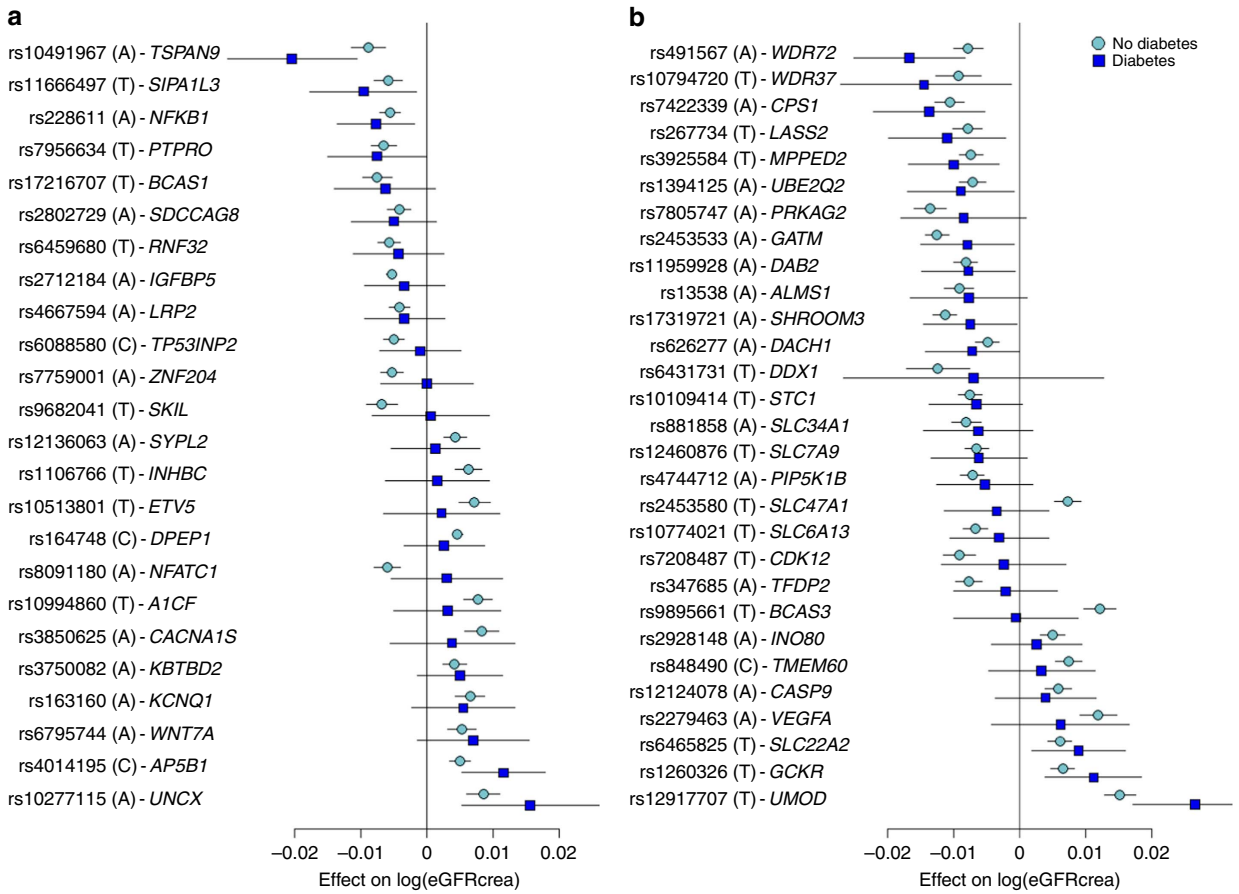


**Figure 2 | Association eGFRcrea loci in subjects with and without diabetes.** Novel (**a**) and known (**b**) loci were considered. Displayed are effects and their 95% confidence intervals on ln(eGFRcrea). Results are sorted by increasing effects in the diabetes group. The majority of loci demonstrated similar effect sizes in the diabetes as compared with non-diabetes strata. SNP-specific information and detailed sample sizes are reported in Supplementary Table 5.

**DNase I hypersensitivity and H3K4m3 chromatin mark analyses.** To evaluate whether eGFRcrea-associated SNPs map into gene regulatory regions and to thereby gain insight into their potential function, we evaluated the overlap of independent eGFRcrea-associated SNPs with $P$ values $<10^{-4}$ (or their proxies) with DHSs using publicly available data from the Epigenomics Roadmap Project and ENCODE for 123 cell types (see Methods). DHSs mark accessible chromatin regions where transcription may occur. Compared with a set of control SNPs (see Methods), eGFRcrea-associated SNPs were significantly more likely to map to DHS in six specific tissues or cell types (Fig. 3b), including adult human renal cortical epithelial cells, adult renal proximal tubule epithelial cells, H7 embryonic stem cells (differentiated 2 days), adult human renal epithelial cells, adult small airway epithelial cells and amniotic epithelial cells. No significant enrichment was observed for adult renal glomerular endothelial cells, the only other kidney tissue evaluated.

Next, we analysed the overlap of the same set of SNPs with H3K4me3 chromatin marks, promoter-specific histone modifications associated with active transcription[24], in order to gather more information about cell-type specific regulatory potential of eGFRcrea-associated SNPs. Comparing 33 available adult-derived cell types, we found that eGFRcrea-associated SNPs showed the most significant overlap with H3K4me3 peaks in adult kidney ($P$ value = 0.0029), followed by liver ($P$ value = 0.0117), and rectal mucosa ($P$ value = 0.0445). Taken together, these findings are suggestive of cell-type-specific regulatory roles for eGFR loci, with greatest specificity for the kidney.

**Chromatin annotation maps.** In addition to assessing individual regulatory marks separately, we annotated the known and replicated novel SNPs, as well as their perfect proxies in a complementary approach. Chromatin annotation maps were generated integrating >10 epigenetic marks from cells derived from adult human kidney tissue and a variety of non-renal tissues from the ENCODE project (see Methods). The proportion of variants to which a function could be assigned was significantly higher when using chromatin annotation maps from renal tissue compared with using maps that investigated the same epigenetic marks in other non-renal tissues (Fig. 3c), again indicating that eGFRcrea associated SNPs are, or tag, kidney-specific regulatory variants. The difference between kidney and non-renal tissues was particularly evident for marks that define enhancers: the proportion of SNPs mapping to weak and strong enhancer regions in the kidney tissue was higher than in all non-kidney tissues (Fishers' exact test $P$ values from $3.1\times10^{-3}$ to $7.9\times10^{-6}$, multiple testing threshold $\alpha=5.6\times10^{-3}$).

**Functional characterization of new loci.** To prioritize genes for functional studies, we applied gene prioritization algorithms including GRAIL[25], DEPICT and manual curation of selected genes in each region (Supplementary Table 12). For each region, gene selection criteria were as follows: (1) either GRAIL $P$ value <0.05 or DEPICT false discovery rate (FDR) <0.05; (2) the effect of a given allele on eGFRcrea and on eGFRcys was direction-consistent and their ratio was between 0.2 and 5

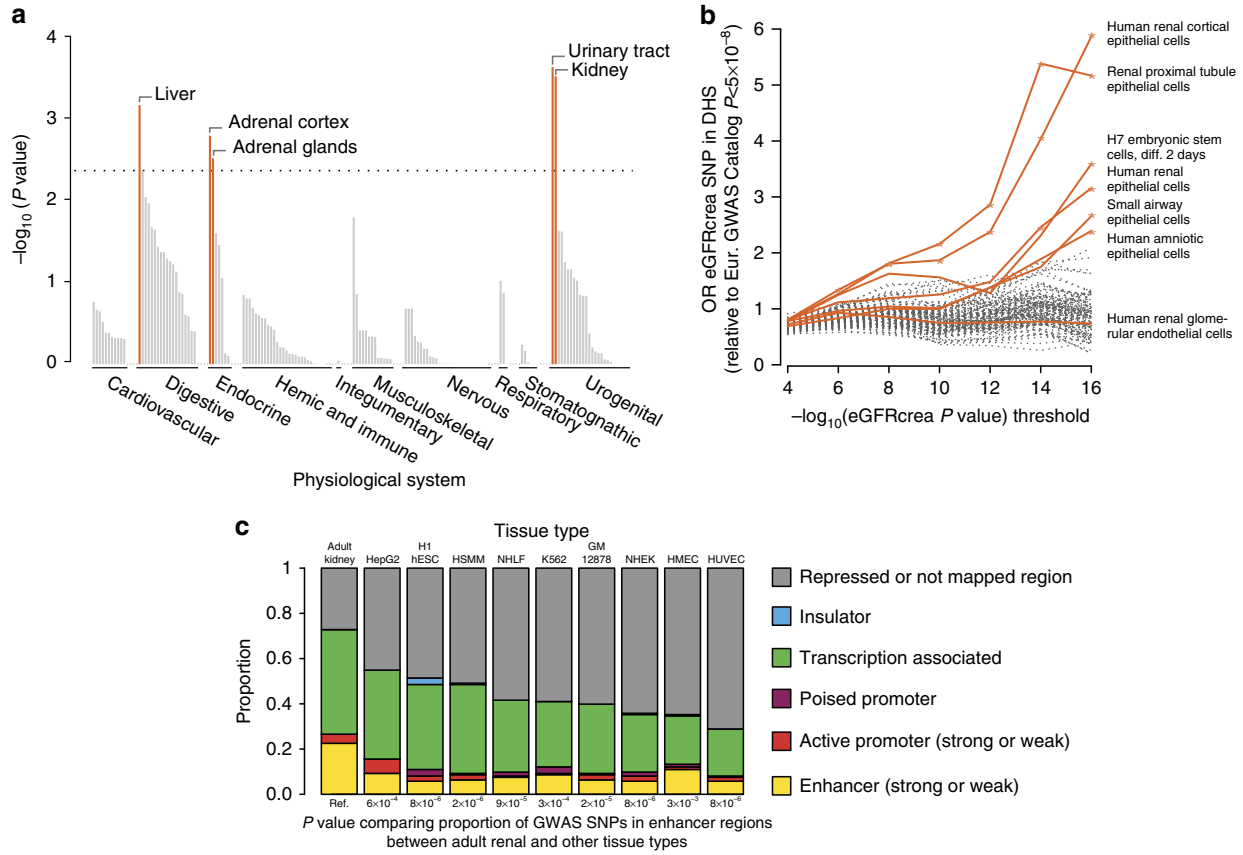


**Figure 3 | Bioinformatic analysis of eGFR-associated SNPs.** Connection of eGFR-associated SNPs to gene expression and variant function across a variety of tissues, pathways and regulatory marks was considered. (**a**) The DEPICT method shows that implicated eGFR-associated genes are highly expressed in particular tissues, including kidney and urinary tract. Shown are permutation test *P* values (see Methods). (**b**) Enrichment of eGFRcrea-associated SNPs in DHS according to discovery *P* value threshold. SNPs from the eGFR discovery genome-wide scan meeting a series of *P* value thresholds in the range $10^{-4}$–$10^{-16}$ preferentially map to DHSs, when compared with a set of control SNPs, in 6 of 123 cell types. Represented are main effects odds ratios from a logistic mixed effect model. Cell types indicated with coloured lines had nominally significant enrichment (* indicate *P* values $<0.05$) at the *P* value $<10^{-16}$ threshold and/or were derived from renal tissues (H7esDiffa2d: H7 embryonic stem cells, differentiated 2 days with BMP4, activin A and bFGF; Hae, amniotic epithelial cells; Hrce, renal cortical epithelial cells; Hre, renal epithelial cells; Hrgec, renal glomerular endothelial cells; Rptec, renal proximal tubule epithelial cells; Saec, small airway epithelial cells). (**c**) ENCODE/Chromatin ChIP-seq mapping: known and replicated novel eGFRcrea-associated SNPs and their perfect proxies were annotated based on genomic location using chromatin annotation maps from different tissues including adult kidney epithelial cells. *P* values from Fishers' exact tests for $2 \times 2$ tables are reported (significance level $= 5.6 \times 10^{-3}$, see Methods). There is significant enrichment of variants mapping to enhancer regions specifically in kidney but not other non-renal tissues.

(to ensure relative homogeneity of the beta coefficients); (3) nearest gene if the signal was located in a region containing a single gene. Using this approach, *NFKB1*, *DPEP1*, *TSPAN9*, *NFATC1*, *WNT7A*, *PTPRO*, *SYPL2*, *UNCX*, *KBTBD2*, *SKIL* and *A1CF* were prioritized as likely genes underlying effects at the new loci (Supplementary Table 12).

We investigated the role of these genes during vertebrate kidney development by examining the functional consequences of gene knockdown in zebrafish embryos utilizing antisense morpholino oligonucleotide (MO) technology. After knockdown, we assessed the expression of established renal markers *pax2a* (global kidney), *nephrin* (podocytes) and *slc20a1a* (proximal tubule) at 48 hours post fertilization by *in situ* hybridization[12]. In all cases, morphant embryos did not display significant gene expression defects compared with controls (Supplementary Table 15).

## Discussion

We identified 24 new loci in association with eGFR and confirmed 29 previously identified loci. A variety of complementary analytic, bioinformatic and functional approaches indicate enrichment of implicated gene products in kidney and urinary tract tissues. A greater proportion of the lead SNPs or their perfect proxies map into gene regulatory regions, specifically enhancers, in adult renal tissues compared with non-renal tissues. In addition to the importance in the adult kidney, our results indicate a role for kidney function variants during development.

We extend our previous findings, as well as those from other groups[7–13] by identifying $>50$ genomic loci for kidney function, many of which were not previously known to be connected to kidney function and disease. Using a discovery data set that is nearly double in size to our prior effort[7], we are now able to robustly link associated SNPs to kidney-specific gene regulatory function. Our work further exemplifies the continued value of increasing the sample size of GWAS meta-analyses to uncover additional loci and gain novel insights into the mechanisms underlying common phenotypes[26].

There are several messages from our work. First, many of the genetic variants associated with eGFR appear to affect processes specifically within the kidney. The kidney is a highly vascular and

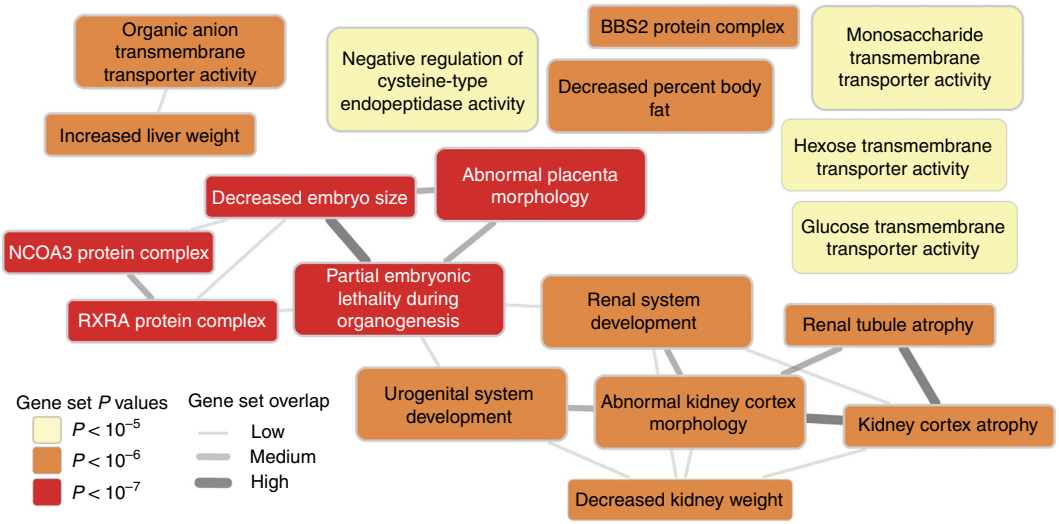


**Figure 4 | Gene set overlap analysis.** The 19 reconstituted gene sets with $P$ value $<10^{-5}$ were considered. Their overlap was estimated by computing the pairwise Pearson correlation coefficient $\rho$ between each pair of gene sets followed by discretization into one of three bins: $0.3 \leq \rho < 0.5$, low overlap; $0.5 \leq \rho < 0.7$, medium overlap; $\rho \geq 0.7$, high overlap. Overlap is shown by edges between gene set nodes and edges representing overlap corresponding to $\rho < 0.3$ are not shown. The network was drawn with Cytoscape[48].

metabolically active organ that receives 20% of all cardiac output, contains an extensive endothelium-lined capillary network, and is sensitive to ischaemic and toxic injury. As a result, hypertension, cardiovascular diseases and diabetes each affect renal hemodynamics and contribute to kidney injury. However, many of the eGFR-associated SNPs in our GWAS could be assigned gene regulatory function specifically in the kidney and its epithelial cells, but not in human glomerular endothelial cells or the general vasculature. In addition, variants associated with eGFR were not associated with vascular traits, such as blood pressure or myocardial infarction. Taken together, these findings suggest that genetic determinants of eGFR may be mediated largely through direct effects within the kidney.

Second, despite the specificity related to renal processes, we also identified several SNPs that are associated with eGFR in diabetes, and our pathway analyses uncovered gene sets associated with glucose transporter activity and abnormal glucose homeostasis. Uncovering *bona fide* genetic loci for diabetic CKD has been difficult. We have now identified a total of 19 SNPs that demonstrate at least nominal association with eGFR in diabetes. The diabetes population is at particularly high risk of CKD, and identifying kidney injury pathways may help develop new treatments for diabetic CKD.

Finally, even though CKD is primarily a disease of the elderly, our pathway enrichment analyses highlight developmental processes relevant to the kidney and the urogenital tract. Kidney disease has been long thought to have developmental origins, in part related to early programming (Barker hypothesis)[27], low birth weight, nephron endowment and early growth and early-life nutrition[28]. Our pathway enrichment analyses suggest that developmental pathways such as placental morphology, kidney weight and embryo size, as well as protein complexes of importance in renal development may in part contribute to the developmental origins of CKD.

A limitation of our work is that causal variants and precise molecular mechanisms underlying the observed associations were not identified and will require additional experimental follow-up projects. Our attempt to gain insights into potentially causal genes through knockdown in zebrafish did not yield any clear CKD candidate gene, although the absence of a zebrafish phenotype upon gene knockdown does not mean that the gene cannot be the one underlying the observed association signal in humans. Finally, our conclusions that eGFRcrea-associated SNPs regulate the expression of nearby genes specifically in kidney epithelial cells are based on DHSs, H3K4me3 chromatin marks and chromatin annotation maps. Since these analyses rely mostly on variant positions, additional functional investigation such as luciferase assay that assess transcriptional activity more directly are likely to gain additional insights into the variants' mechanism of action.

The kidney specificity for loci we identified may have important translational implications, particularly since our DHS and chromatin annotation analyses suggest that at least a set of gene regulatory mechanisms is important in the adult kidney. Kidney-specific pathways are important for the development of novel therapies to prevent and treat CKD and its progression with minimal risk of toxicity to other organs. Finally, the biologic insights provided by these new loci may help elucidate novel mechanisms and pathways implicated not only in CKD but also of kidney function in the physiological range.

In conclusion, we have confirmed 29 genomic loci and identified 24 new loci in association with kidney function that together highlight target organ-specific regulatory mechanisms related to kidney function.

## Methods

**Overview.** This was a collaborative meta-analysis with a distributive data model. Briefly, an analysis plan was created and circulated to all participating studies. Studies then uploaded study-specific data centrally; files were cleaned, and a specific meta-analysis for each trait was performed. Details regarding each step are provided below. All participants in all discovery and replication studies provided informed consent. Each study had its research protocol approved by the local ethics committee.

**Phenotype definitions.** Serum creatinine was measured in each discovery and replication study as described in Supplementary Tables 16 and 17, and statistically calibrated to the US nationally representative National Health and Nutrition Examination Study data in all studies to account for between-laboratory variation[9,29,30]. eGFRcrea was estimated using the four-variable Modification of Diet in Renal Disease Study Equation. Cystatin C, an alternative biomarker for kidney function, was measured in a sub-set of participating studies. eGFRcys was estimated as $76.7 \times (\text{serum cystatin C})^{-1.19}$ (ref. 31). eGFRcrea and eGFRcys values

$<15$ ml min per 1.73 $m^2$ were set to 15, and those $>200$ were set to 200 ml $min^{-1}$ per 1.73 $m^2$. CKD was defined as eGFRcrea $<60$ ml $min^{-1}$ per 1.73 $m^2$.

Diabetes was defined as fasting glucose $\geq 126$ mg $dl^{-1}$, pharmacologic treatment for diabetes or by self-report. In all studies, diabetes and kidney function were assessed at the same point in time.

**Genotypes.** Genotyping was conducted in each study as specified in Supplementary Tables 18 and 19. After applying appropriate quality filters, 45 studies used markers of highest quality to impute $\sim$2.5 million SNPs, based on European-ancestry haplotype reference samples (HapMap II CEU). Four studies based their imputation on the 1000 Genomes Project data. Imputed genotypes were coded as the estimated number of copies of a specified allele (allelic dosage).

**Genome-wide association analysis.** By following a centralized analysis plan, each study regressed sex- and age-adjusted residuals of the logarithm of eGFRcrea or eGFRcys on SNP dosage levels. Logistic regression of CKD status was performed on SNP dosage levels adjusting for sex and age. For all traits, adjustment for appropriate study-specific features, including study site and genetic principal components was included in the regression and family-based studies appropriately accounted for relatedness.

**Stage 1 discovery meta-analysis.** GWAS of eGFRcrea were contributed by 48 studies (total sample size, $N=133{,}413$); 45 studies contributed GWAS data for the non-diabetes subgroup ($N=118{,}448$) and 39 for the diabetes group ($N=11{,}522$). GWAS of CKD were comprised by 43 studies, for a total sample size of 117,165, including 12,385 CKD cases. GWAS of eGFRcys were comprised by 16 studies for a total sample size of 32,834. All GWAS files underwent quality control using the GWAtoolbox package[32] in R, before including them into the meta-analysis. Genome-wide meta-analysis was performed with the software METAL[33], assuming fixed effects and using inverse-variance weighting. The genomic inflation factor $\lambda$ was estimated for each study as the ratio between the median of all observed test statistics $(b/\text{s.e.})^2$ and the expected median of a $\chi^2$ with 1 degree of freedom, with $b$ and s.e. representing the effect of each SNP on the phenotype and its standard error, respectively[34]. Genomic-control (GC) correction was applied to $P$ values and s.e.'s in case of $\lambda>1$ (first GC correction). SNPs with an average minor allele frequency (MAF) of $\geq 0.01$ were used for the meta-analysis. To limit the possibility of false positives, after the meta-analysis, a second GC correction on the aggregated results was applied. Between-study heterogeneity was assessed through the $I^2$ statistic.

After removing SNPs with MAF of $<0.05$ and which were available in $<50\%$ of the studies, SNPs with a $P$ value of $\leq 10^{-6}$ were selected and clustered into independent loci through LD pruning based on an $r^2$ of $\leq 0.2$ within a window of $\pm 1$ MB to each side of the index SNP. After removing loci containing variants that have been previously replicated at a $P$ value of $5.0\times10^{-8}$ (refs 7,8), the SNP with the lowest $P$ value within each locus was selected for replication ('index SNP'). If a SNP had an association $P$ value of $\leq 10^{-6}$ with more than one trait, the trait where the SNP had the lowest $P$ value was selected as discovery trait/stratum. Altogether, this resulted in 48 SNPs: 34 from eGFRcrea, 9 from eGFRcrea among those without diabetes, 4 from CKD and 1 from eGFRcys.

**Stage 2 replication analysis.** *In silico* replication analysis for any of the studied traits was carried out using eight independent studies whose genotyping platforms are provided in Supplementary Table 19. *De novo* genotyping was performed in seven additional studies ($N=22{,}850$ individuals) of European ancestry (Supplementary Table 20), including the Bus Santé, ESTHER, KORA-F3 (subset of F3 without GWAS), KORA-F4 (subset of F4 without GWAS), Ogliastra Genetic Park (OGP, without Talana whose GWAS was included in the discovery analysis), SAPHIR and SKIPOGH studies (Supplementary Table 20). Summarizing all *in silico* and *de novo* replication studies (Supplementary Table 1), replication data for eGFRcrea were contributed by 14 studies (total sample size $=42{,}166$), which also contributed eGFRcrea results from non-diabetes (13 studies, $N=36{,}433$) and diabetes samples (13 studies, $N=4{,}955$). Thirteen studies contributed replication data on CKD ($N=33{,}972$; 4,245 CKD cases; studies with $<50$ CKD cases were excluded) and five on eGFRcys ($N=14{,}930$).

Association between eGFRcrea, CKD and eGFRcys and each of the 48 SNPs in the replication studies was assessed using the same analysis protocol detailed for the discovery studies above. Quality control of the replication files was performed with the same software as described above.

We performed a combined fixed-effect meta-analysis of the double-GC corrected results from the discovery meta-analysis and the replication studies, based on inverse-variance weighting. The total sample size in the combined analysis of eGFRcrea was 175,579 subjects (154,881 in the non-diabetes stratum and 16,477 in the diabetes stratum; the sum of these two sample sizes is smaller than the sample size of the overall analysis because some studies did not contribute both strata), 151,137 samples for CKD (16,630 CKD cases) and 47,764 for eGFRcys. Three criteria were used to ensure validity of novel loci declared as significant: (1) $P$ value from the combined meta-analysis $\leq 5.0\times10^{-8}$ in accordance with previously published guidelines[35]; (2) direction-consistent associations of the beta coefficients in stage 1 and stage 2 (one-sided $P$ values were estimated to test for consistent effect direction with the discovery stage); (3) $q$-value $<0.05$ in the replication stage. Q-values were estimated using the package QVALUE[36] in R. The tuning parameter lambda for the estimation of the overall proportion of true null hypotheses, $\pi0$, was estimated using the bootstrap method[37]. When the third criterion was not satisfied, the locus was declared 'suggestive'.

**Power analysis.** With the sample size achieved in the combined analysis of stage 1 and stage 2 data, the power to assess replication at the canonical genome-wide significance level of $5.0\times10^{-8}$ was estimated with the software QUANTO[38] version 1.2.4, assuming the same MAF and effect size observed in the discovery sample. Power to replicate associations ranged from 87 to 100% for eGFRcrea associated SNPs (median $=98\%$), from 72 to 96% for the CKD-associated SNPs, and was equal to 59% for the eGFRcys-associated SNP (Supplementary Table 3).

**Associations stratified by diabetes and hypertension status.** For all the 24 novel and 29 known SNPs, the difference between the SNP effect on eGFRcrea in the diabetes versus the non-diabetes groups was assessed by means of a two-sample $t$-test for correlated data at a significance level of 0.05. We used the following two-sample $t$-test for correlated data:

$$t=\frac{(b_{\mathrm{DM}}-b_{\mathrm{nonDM}})}{\left\{\text{s.e.}(b_{\mathrm{DM}})^2+\text{s.e.}(b_{\mathrm{nonDM}})^2-2\times\rho(b_{\mathrm{DM}},b_{\mathrm{nonDM}})\times\text{s.e.}(b_{\mathrm{DM}})\times\text{s.e.}(b_{\mathrm{nonDM}})\right\}^{0.5}},$$

where $b_{\mathrm{DM}}$ and $b_{\mathrm{nonDM}}$ represent the SNP effects on log(eGFRcrea) in the two groups, s.e. is the standard error of the estimate and $\rho(.)$ indicates the correlation between effects in the two groups, which was estimated as 0.044 by sampling 100,000 independent SNPs from our DM and nonDM GWAS, after removing known and novel loci associated with eGFRcrea. For a large sample size, as in our case, $t$ follows a standard normal distribution.

A similar analysis was performed to compare results in subjects with and without hypertension, based on results from our previous work[7]. The correlation between the two strata was of 0.01.

**Proportion of phenotypic variance explained.** The percent of phenotypic variance explained by novel and known loci was estimated as $\sum_{i=1}^{53}R_i^2$, where $R_i^2=b_i^2\mathrm{var}(\mathrm{SNP}_i)/\mathrm{var}(y)$ is the coefficient of determination for each of the 53 individual SNPs associated with eGFRcrea uncovered to date (24 novel and 29 known ones), $b_i$ is the estimated effect of the $i^{\mathrm{th}}$ SNP on $y$, $y$ corresponds to the sex- and age-adjusted residuals of the logarithm of eGFRcrea and $\mathrm{var}(\mathrm{SNP_i})=2\times\mathrm{MAF_{SNPi}}\times(1-\mathrm{MAF_{SNPi}})$[39]. Var($y$) was estimated in the ARIC study and all loci were assumed to have independent effects on the phenotype.

**Test for SNP associations with related traits.** We performed evaluations of SNP association with results generated from consortia investigating other traits. Specifically, we evaluated systolic and diastolic blood pressure in ICBP[17], myocardial infarction in CARDiOGRAM[18], left ventricular mass[19], heart failure[20], the urinary albumin to creatinine ratio (CKDGen consortium, personal communication) and fasting plasma glucose in MAGIC[21]. In total, we performed 165 tests, corresponding to 7 traits tested for association against each of the 24 novel SNP, with the exception of myocardial infarction for which results from 3 SNPs were not available (Supplementary Table 6). Significance was evaluated at the Bonferroni corrected level of $0.05/165=0.0003$.

**Lookup of replicated loci in the NHGRI GWAS catalog.** All replicated SNPs, as well as SNPs in LD ($r^2>0.2$) within $\pm 1$ MB distance were checked for their association with other traits according to the NHGRI GWAS catalog[40] (accessed April 14, 2014).

**SNP assessments in other ethnic groups.** We performed cross-ethnicity SNP evaluations in participants of African ancestry from a meta-analysis of African ancestry individuals and from participants of Asian descent from the AGEN consortium[11].

**African ancestry meta-analysis.** We performed fixed-effect meta-analysis of the genome-wide association data from 12 African ancestry studies (Supplementary Table 8) with imputation to HapMap reference panel, based on inverse-variance weighting using METAL. Only SNPs with MAF $\geq 0.01$ and imputation quality $r^2\geq 0.3$ were considered for the meta-analysis. After meta-analysis, we removed SNPs with MAF $<0.05$ and which were available in $<50\%$ of the studies. Statistical significance was assessed at the standard threshold of $5.0\times10^{-8}$. Genomic control correction was applied at both the individual study level before meta-analysis and after the meta-analysis.

**Transethnic meta-analysis.** We performed a trans-ethnic meta-analysis of GWAS data from cohorts of different ethnic backgrounds using MANTRA (Meta-Analysis

of Trans-ethnic Association studies) software[22]. We combined the 48 European ancestry studies that contributed eGFRcrea, which were included in stage 1 discovery meta-analysis, and the 12 African ancestry studies mentioned above for a total sample size of 150,253 samples. We limited our analysis to biallelic SNPs with MAF $\geq$0.01 and imputation quality $r^2 \geq 0.3$. Relatedness between the 60 studies was estimated using default settings from up to 5.9 million SNPs. Only SNPs that were present in more than 25 European ancestry studies and 6 African ancestry studies (total sample size $\geq$120,000) were considered after meta-analysis. Genome-wide significance was defined as a $\log_{10}$ Bayes' Factor ($\log_{10}$BF) $\geq$6 (ref. 41).

**Gene Relationships Across Implicated Loci (GRAIL).** To prioritize the gene(s) most likely to give rise to association signals in a given region, the software GRAIL was used[25]. The index SNP of all previously known kidney function associated regions, as well as the novel SNPs identified here was used as input, using the CEU HapMap (hg18 assembly) and the functional datasource text_2009_03, established before the publication of kidney function-related GWAS. Results from GRAIL were used to prioritize genes for follow-up functional work.

**Expression quantitative trait loci analysis.** We identified alias rsIDs and proxies ($r^2 > 0.8$) for our index SNPs using SNAP software across 4 HapMap builds. SNP rsIDs and aliases were searched for primary SNPs and LD proxies against a collected database of expression SNP (eSNP) results. The collected eSNP results met criteria for statistical thresholds for association with gene transcript levels in their respective original analyses (for references see Supplementary Table 11). Correlation of selected eSNPs to the best eSNPs per transcript per expression quantitative trait loci (eQTL) data set were assessed by pairwise LD. All results are reported in Supplementary Table 11.

**DEPICT analysis.** In this work, we first used PLINK[42] to identify independently associated SNPs using all SNPs with eGFRcrea association $P$ values $<10^{-5}$ (HapMap release 27 CEU data[43]; LD $r^2$ threshold = 0.01; physical kb threshold = 1,000). We then used the DEPICT method[23] to construct associated regions by mapping genes to independently associated SNPs if they overlapped or resided within LD ($r^2 > 0.5$) distance of a given associated SNP. After merging overlapping regions and discarding regions that mapped within the major histocompatibility complex locus (chromosome 6, base pairs 20,000,000–40,000,000), 124 non-overlapping regions remained that covered a total of 320 genes. Finally, we ran the DEPICT software program on the 124 regions to prioritize genes that may represent promising candidates for experimental follow up studies, identify reconstituted gene sets that are enriched in genes from associated regions and therefore may provide insight into general kidney function biology, and identify tissue and cell-type annotations in which genes from associated regions are highly expressed. Specifically, for each tissue, the DEPICT method performs a $t$-test comparing the tissue-specific expression of eGFRcrea-associated genes and all other genes. Next, for each tissue, empirical enrichment $P$ values are computed by repeatedly sampling random sets of loci (matched to the actual eGFRcrea loci by gene density) from the entire genome to estimate the empirical mean and s.d. of the enrichment statistic's null distribution. To visualize the nineteen reconstituted gene sets with $P$ value $<1e-5$ (Fig. 4), we estimated their overlap by computing the pairwise Pearson correlation coefficient $\rho$ between each pair of gene sets followed by discretization into one of three bins; $0.3 \leq \rho < 0.5$, low overlap; $0.5 \leq \rho < 0.7$, medium overlap; $\rho \geq 0.7$, high overlap.

**DNase I hypersensitivity analysis.** The overlap of SNPs associated with eGFRcrea at $P<10^{-4}$ with DHSs was examined using publically available data from the Epigenomics Roadmap Project and ENCODE. In all, DHS mappings were available for 123 mostly adult cells and tissues[44] (downloaded from http://hgdownload.cse.ucsc.edu/goldenPath/hg19/encodeDCC/wgEncodeUwDnase/). The analysis here pertains to DHS's defined as 'broad' peaks, which were available as experimental replicates (typically duplicates) for the majority of cells and tissues.

SNPs from our stage 1 eGFRcrea GWAS meta-analysis were first clumped in PLINK[42] in windows of 100 kb and maximum $r^2$ of 0.1 using LD relationships from the 1,000 Genomes EUR panel (phase I, v3, 3/14/2012 haplotypes) using a series of $P$ value thresholds ($10^{-4}$, $10^{-6}$, $10^{-8}$, ... and $10^{-16}$). LD proxies of the index SNPs from the clumping procedure were then identified by LD tagging in PLINK with $r^2 = 0.8$ in windows of 100 kb, again using LD relationships in the 1000G EUR panel, restricted to SNPs with MAF >1% and also present in the HapMap2 CEU population. A reference set of control SNPs was constructed using the same clumping and tagging procedures applied to NHGRI GWAS catalog SNPs (available at http://www.genome.gov/gwastudies/, accessed 13 March 2013) with discovery $P$ values $<5.0 \times 10^{-8}$ in European populations. In total, there were 1,204 such reference SNPs after LD pruning. A small number of reference SNPs or their proxies overlapping with the eGFRcrea SNPs or their proxies were excluded. For each cell-type and $P$ value threshold, the enrichment of eGFR SNPs (or their LD proxies) mapping to DHSs relative to the GWAS catalog reference SNPs (or their LD proxies) was expressed as an odds ratio from logistic mixed effect models that treated the replicate peak determinations as random effects (lme4 package in R). Significance for enrichment odds ratio was derived from the significance of beta coefficients for the main effects in the mixed models.

**Interrogation of human kidney chromatin annotation maps.** Different chromatin modification patterns can be used to generate tissue-specific chromatin-state annotation maps. These can serve as a valuable resource to discover regulatory regions and study their cell-type-specific distributions and activities, which may help with the interpretation especially of intergenic variants identified in association studies[45]. We therefore investigated the genomic mapping of the known and replicated novel index SNPs, as well as their perfect LD proxies ($n = 173$, $r^2 = 1$ for proxies) using a variety of resources, including chromatin maps generated from human kidney tissue cells (HKC-E cells). Chromatin immune-precipitation sequencing (ChIP-seq) data from human kidney samples were generated by NIH Roadmap Epigenomics Mapping Consortium[46]. Briefly, proximal tubule cells derived from an adult human kidney were collected and cross-linked with 1% formaldehyde. Subsequently, ChIP-seq was conducted using whole-cell extract from adult kidney tissue as the input (GSM621638) and assessing the following chromatin marks: H3K36me3 (GSM621634), H3K4me1 (GSM670025), H3K4me3 (GSM621648), H3K9ac (GSM772811) and H3K9me3 (GSM621651). The MACS version 1.4.1 (model-based analysis of ChIP-Seq) peak-finding algorithm was used to identify regions of ChIP-Seq enrichment[47]. A FDR threshold of enrichment of 0.01 was used for all data sets. The resulting genomic coordinates in bed format were further used in ChromHMM v1.06 for chromatin annotation[45]. For comparison, the same genomic coordinates were investigated in chromatin annotation maps of renal tissue, as well as across nine different cell lines from the ENCODE Project: umbilical vein endothelial cells (HUVEC), mammary epithelial cells (HMEC), normal epidermal keratinocytes (NHEK), B-lymphoblastoid cells (GM12878), erythrocytic leukemia cells (K562), normal lung fibroblasts (NHLF), skeletal muscle myoblasts (HSMM), embryonic stem cells (H1 ES) and hepatocellular carcinoma cells (HepG2). We tested whether the proportion of SNPs pointing to either strong or weak enhancers in the human kidney tissue cells was different from that of the other nine tissues by means of a Fishers' exact test for $2 \times 2$ tables, contrasting each of the nine cell lines listed above against the reference kidney cell line, at a Bonferroni-corrected significance level of $0.05/9 = 5.6 \times 10^{-3}$.

**Functional characterization of new loci.** Replicated gene regions were prioritized for functional studies using the following criteria: (1) GRAIL identification of a gene in each region of $P$ value $<0.05$ or DEPICT, FDR $<0.05$); (2) an eGFRcrea to eGFRcys ratio between 0.2 and 5 with direction consistency between the beta coefficients; (3) nearest gene if the signal was located in a gene-poor region. The list of genes selected for functional work can be found in Supplementary Table 12. This same prioritization scheme was also used to assign locus names. Morpholino knockdowns were performed in zebrafish.

Zebrafish (strain Tübingen, TU) were maintained according to established Harvard Medical School Institutional Animal Care and Use Committee protocols (protocol # 04626). Male and female fish were mated (age 6–12 months) for embryo production. Embryos were injected at the one-cell stage with MOs (GeneTools) designed to block either the ATG start site or an exon–intron splice site of the target gene (Supplementary Table 21). In cases where human loci are duplicated in zebrafish, both orthologues were knocked down simultaneously by combination MO injection. MOs were injected in escalating doses at concentrations up to 250 µM. Embryos were fixed in 4% paraformaldehyde at 48 h post fertilization for *in situ* hybridization using published methods (http://zfin.org/ZFIN/Methods/ThisseProtocol.html). Gene expression was visualized using established renal markers *pax2a* (global kidney), *nephrin* (podocytes) and *slc20a1a* (proximal tubule). The number of morphant embryos displaying abnormal gene expression was compared with control embryos by means of a Fisher's exact test.

## References


1. Eckardt, K. U. *et al.* Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* **382,** 158–169 (2013).
2. El Nahas, M. The global challenge of chronic kidney disease. *Kidney Int.* **68,** 2918–2929 (2005).
3. Baumeister, S. E. *et al.* Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. *Am. J. Nephrol.* **31,** 222–229 (2010).
4. Fox, C. S. *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* **380,** 1662–1673 (2012).
5. Mahmoodi, B. K. *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet* **380,** 1649–1661 (2012).
6. Himmelfarb, J. & Tuttle, K. R. New therapies for diabetic kidney disease. *N. Engl. J. Med.* **369,** 2549–2550 (2013).
7. Pattaro, C. *et al.* Genome-wide association and functional follow-up reveals new loci for kidney function. *PLoS Genet.* **8,** e1002584 (2012).
8. Kottgen, A. *et al.* New loci associated with kidney function and chronic kidney disease. *Nat. Genet.* **42,** 376–384 (2010).
9. Kottgen, A. *et al.* Multiple loci associated with indices of renal function and chronic kidney disease. *Nat. Genet.* **41,** 712–717 (2009).
10. Chambers, J. C. *et al.* Genetic loci influencing kidney function and chronic kidney disease. *Nat. Genet.* **42,** 373–375 (2010).

11. Okada, Y. *et al.* Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. *Nat. Genet.* **44,** 904–909 (2012).
12. Liu, C. T. *et al.* Genetic association for renal traits among participants of African ancestry reveals new loci for renal function. *PLoS Genet.* **7,** e1002264 (2011).
13. Boger, C. A. *et al.* Association of eGFR-Related Loci Identified by GWAS with Incident CKD and ESRD. *PLoS Genet.* **7,** e1002292 (2011).
14. Chasman, D. I. *et al.* Integration of genome-wide association studies with biological knowledge identifies six novel genes related to kidney function. *Hum. Mol. Genet.* **21,** 5329–5343 (2012).
15. Pattaro, C. *et al.* A meta-analysis of genome-wide data from five European isolates reveals an association of COL22A1, SYT1, and GABRR2 with serum creatinine level. *BMC Med. Genet.* **11,** 41 (2010).
16. Trudu, M. *et al.* Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat. Med.* **19,** 1655–1660 (2013).
17. International Consortium for Blood Pressure Genome-Wide Association Studies *et al.* Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **478,** 103–109 (2011).
18. Schunkert, H. *et al.* Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat. Genet.* **43,** 333–338 (2011).
19. Vasan, R. S. *et al.* Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. *JAMA* **302,** 168–178 (2009).
20. Smith, N. L. *et al.* Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium. *Circ. Cardiovasc. Genet.* **3,** 256–266 (2010).
21. Dupuis, J. *et al.* New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat. Genet.* **42,** 105–116 (2010).
22. Morris, A. P. Transethnic meta-analysis of genomewide association studies. *Genet. Epidemiol.* **35,** 809–822 (2011).
23. Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6,** 5890 (2015).
24. Trynka, G. *et al.* Chromatin marks identify critical cell types for fine mapping complex trait variants. *Nat. Genet.* **45,** 124–130 (2013).
25. Raychaudhuri, S. *et al.* Identifying relationships among genomic disease regions: predicting genes at pathogenic SNP associations and rare deletions. *PLoS Genet.* **5,** e1000534 (2009).
26. Panagiotou, O. A., Willer, C. J., Hirschhorn, J. N. & Ioannidis, J. P. The power of meta-analysis in genome-wide association studies. *Annu. Rev. Genomics Hum. Genet.* **14,** 441–465 (2013).
27. Barker, D. J. The fetal and infant origins of adult disease. *BMJ* **301,** 1111 (1990).
28. Boubred, F. *et al.* Developmental origins of chronic renal disease: an integrative hypothesis. *Int. J. Nephrol.* **2013,** 346067 (2013).
29. Fox, C. S. *et al.* Predictors of new-onset kidney disease in a community-based population. *JAMA* **291,** 844–850 (2004).
30. Coresh, J. *et al.* Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am. J. Kidney Dis.* **39,** 920–929 (2002).
31. Stevens, L. A. *et al.* Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am. J. Kidney Dis.* **51,** 395–406 (2008).
32. Fuchsberger, C., Taliun, D., Pramstaller, P. P. & Pattaro, C. CKDGen consortium. GWAtoolbox: an R package for fast quality control and handling of GWAS meta-analysis data. *Bioinformatics* **28,** 444–445 (2012).
33. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26,** 2190–2191 (2010).
34. Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55,** 997–1004 (1999).
35. Skol, A. D., Scott, L. J., Abecasis, G. R. & Boehnke, M. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. *Nat. Genet.* **38,** 209–213 (2006).
36. Storey, J. D. A direct approach to false discovery rates. *J. R. Stat. Soc. B* **64,** 479–498 (2002).
37. Storey, J. D., Taylor, J. E. & Siegmund, D. Strong control, conservative point estimation, and simultaneous conservative consistency of false discovery rates: a unified approach. *J. R. Stat. Soc. B* **66,** 187–205 (2004).
38. Gauderman, W. J. Sample size requirements for matched case-control studies of gene-environment interaction. *Stat. Med.* **21,** 35–50 (2002).
39. Rosner, B. in *Fundamentals of Biostatistics* (Thomson-Brooks/Cole, Duxbury, 2006).
40. Welter, D. *et al.* The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res.* **42,** D1001–D1006 (2014).
41. Wang, X. *et al.* Comparing methods for performing trans-ethnic meta-analysis of genome-wide association studies. *Hum. Mol. Genet.* **22,** 2303–2311 (2013).
42. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81,** 559–575 (2007).
43. International HapMap Consortium. The International HapMap Project. *Nature* **426,** 789–796 (2003).
44. Maurano, M. T. *et al.* Systematic localization of common disease-associated variation in regulatory DNA. *Science* **337,** 1190–1195 (2012).
45. ENCODE Project Consortium *et al.* An integrated encyclopedia of DNA elements in the human genome. *Nature* **489,** 57–74 (2012).
46. Ko, Y. A. *et al.* Cytosine methylation changes in enhancer regions of core pro-fibrotic genes characterize kidney fibrosis development. *Genome Biol.* **14,** R108 (2013).
47. Zhang, Y. *et al.* Model-based analysis of ChIP-Seq (MACS). *Genome Biol.* **9,** R137 (2008).
48. Shannon, P. *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.* **13,** 2498–2504 (2003).


## Acknowledgements

Study-specific acknowledgements and funding sources for participating studies are reported in Supplementary Note. Zebrafish work was supported by NIH R01DK090311 and R24OD017870 to W.G.

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## Additional information

**Supplementary Information** accompanies this paper at http://www.nature.com/naturecommunications

**Competing financial interests:** J.T. and P.H. are consultants for Servier. J.C. received research grants and honoraria from Servier. K.S. obtained research support from Boehringer Ingelheim. The remaining authors declared no competing financial interests.

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**How to cite this article:** Pattaro, C. *et al.* Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat. Commun.* 7:10023 doi: 10.1038/ncomms10023 (2016).



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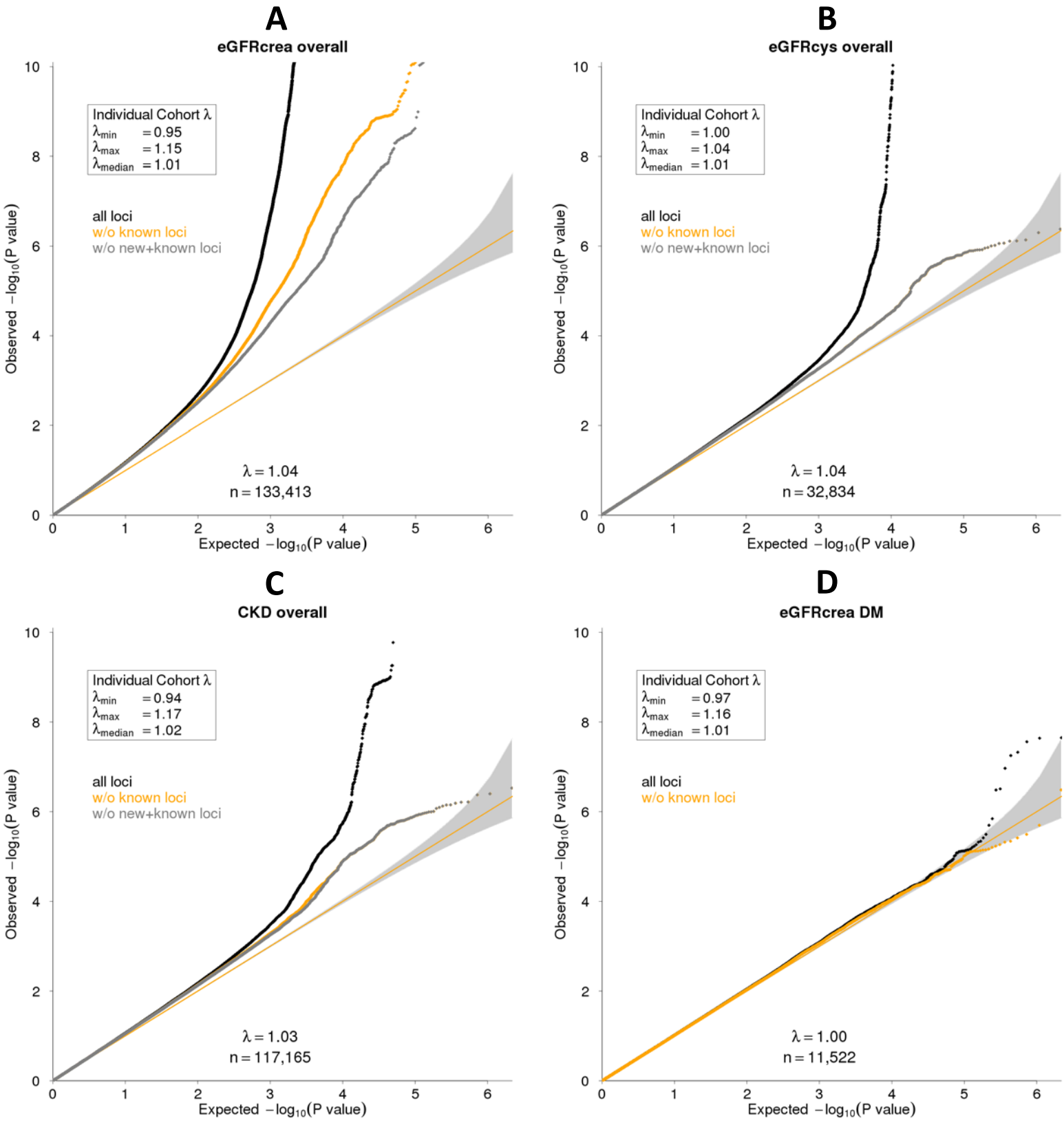
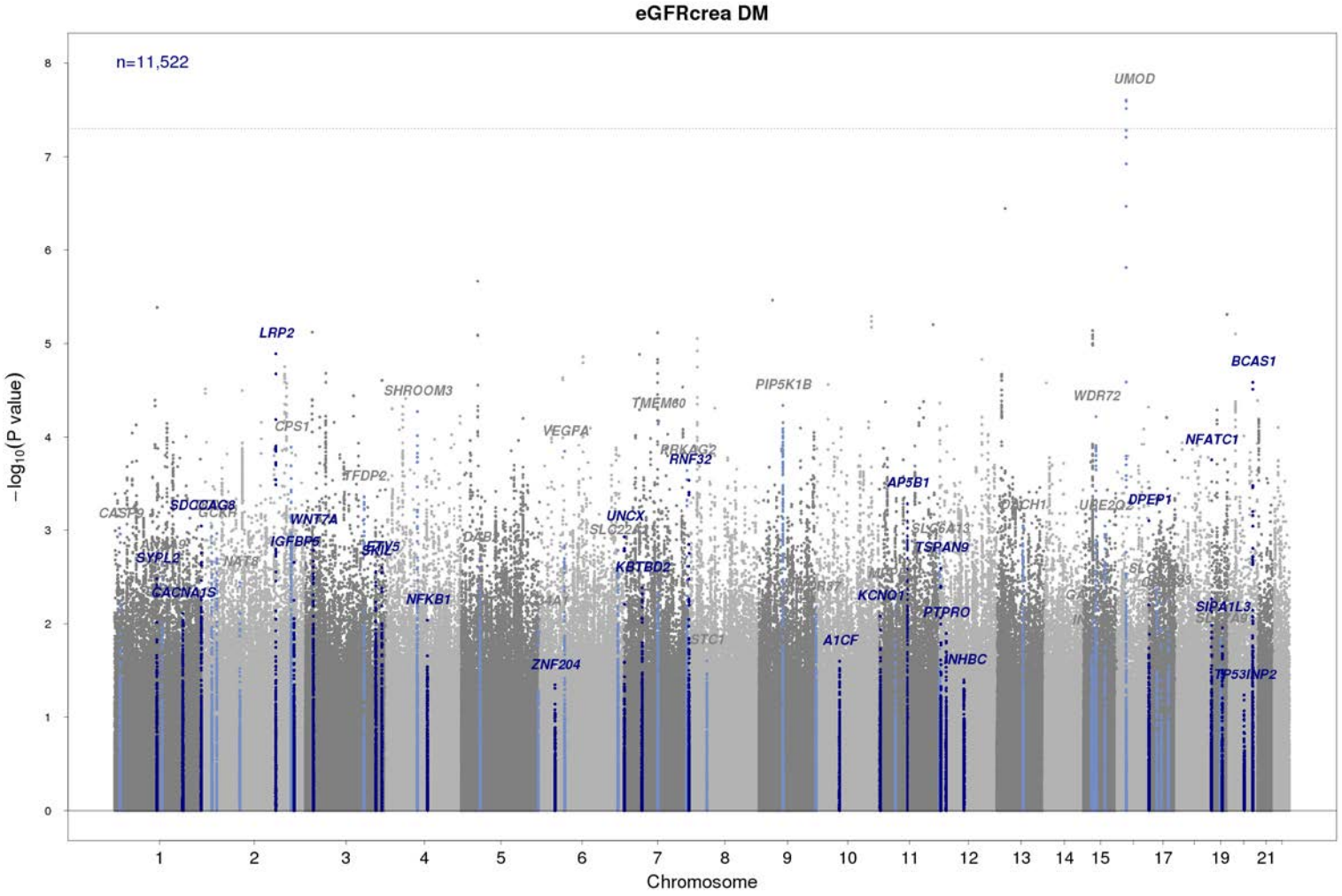
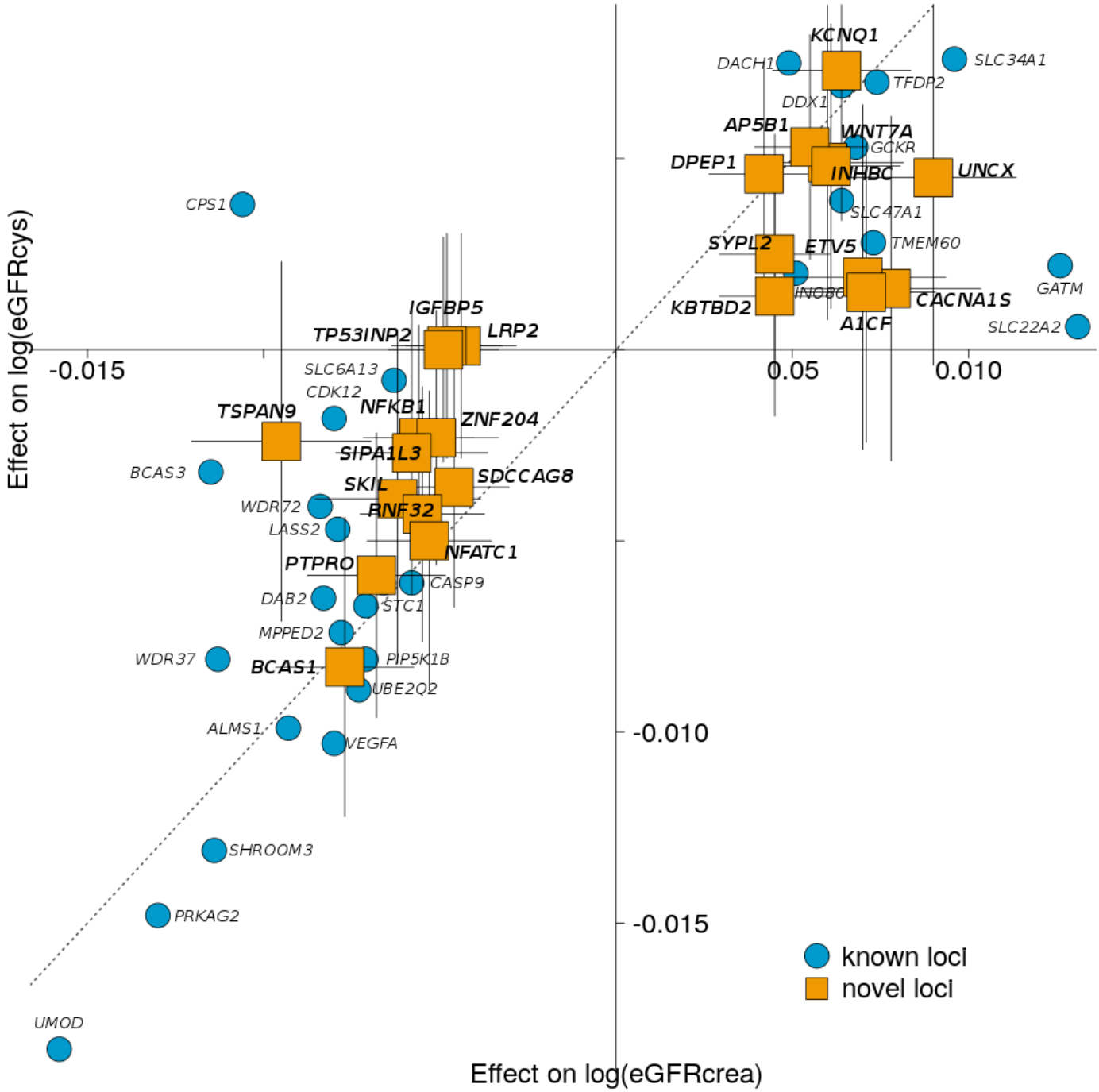
**Supplementary Figure 1**. Q-Q plots of eGFRcrea (**A**), eGFRcys (**B**), CKD (**C**), and eGFRcrea in diabetes (**D**). $\lambda_{1000}$ = 1.00 for all four analyses.[1, 2]



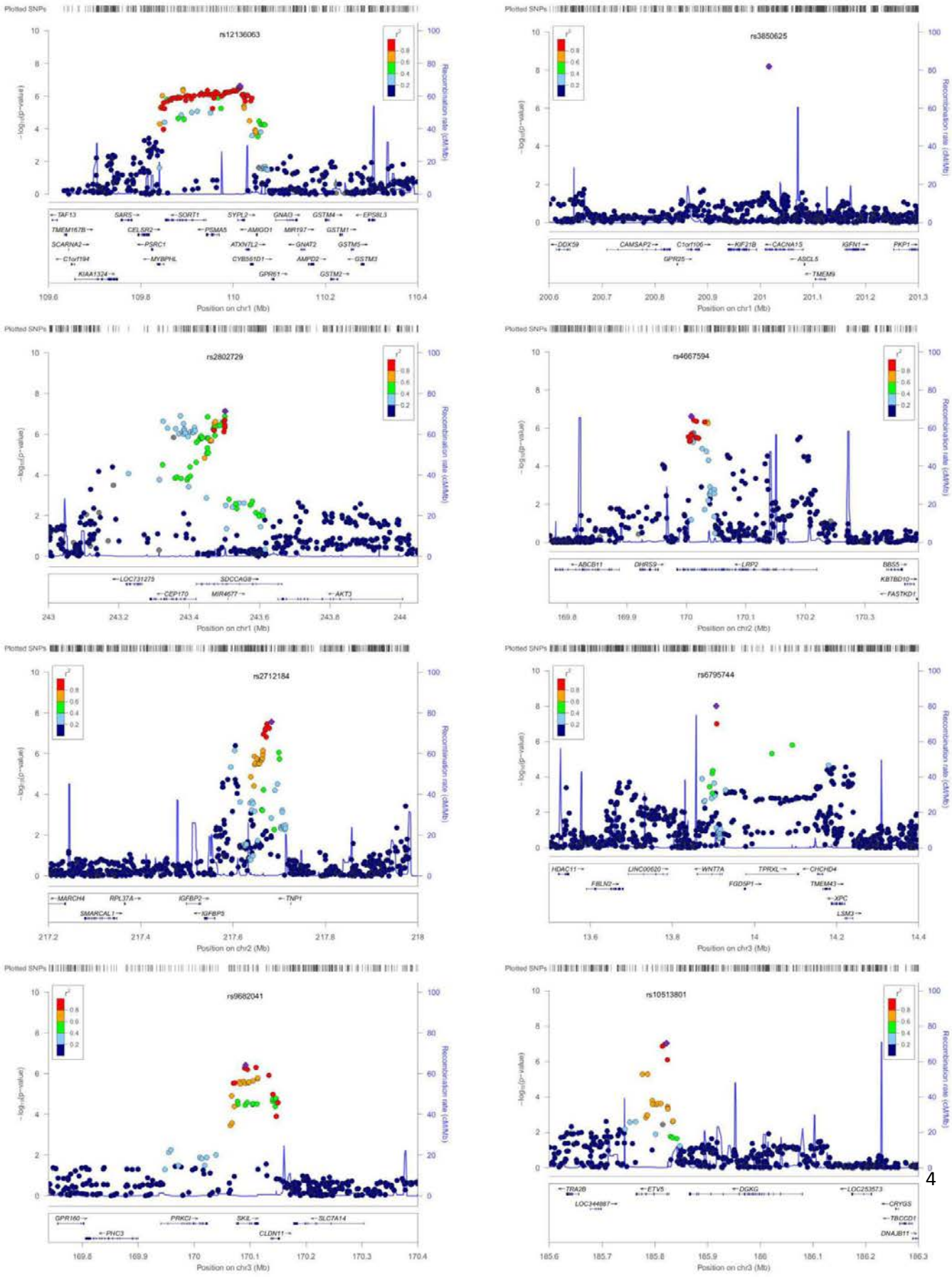
**Supplementary Figure 2**. Manhattan Plots of eGFRcrea in diabetes.

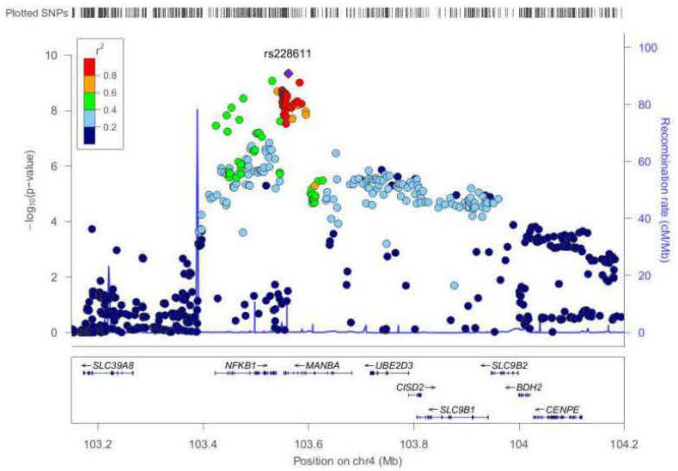


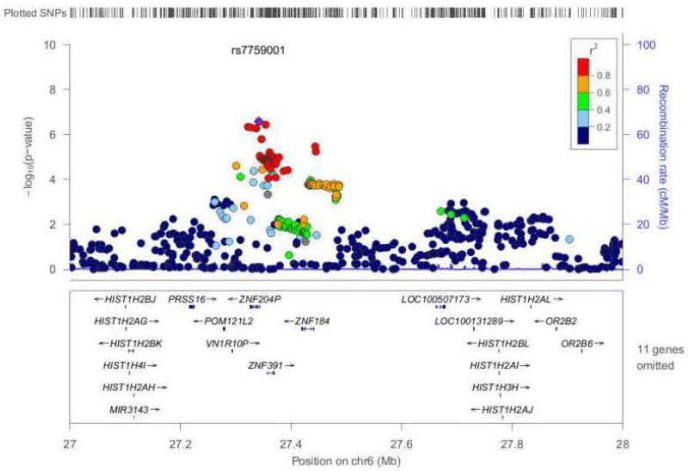
**Supplementary Figure 3**. All replicated loci comparing the effect sizes for eGFRcrea vs eGFRcys; known loci are in blue, new loci are in orange. 95% confidence intervals appear for the new loci only.



**Supplementary Figure 4**. Regional association plots for all 24 novel loci.




Plotted SNPs
rs228611
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
SLC39A8
NFKB1
MANBA
UBE2D3
SLC9B2
CISD2
BDH2
SLC9B1
CENPE
103.2
103.4
103.6
103.8
104
104.2
Position on chr4 (Mb)


Plotted SNPs
rs7759001
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
HIST1H2BJ
PRSS16
ZNF204P
LOC100507173
HIST1H2AL
HIST1H2AG
POM121L2
ZNF184
LOC100131289
OR2B2
HIST1H2BK
VN1R10P
HIST1H2BL
OR2B6
HIST1H4I
ZNF391
HIST1H2AI
HIST1H2AH
HIST1H3H
MIR3143
HIST1H2AJ
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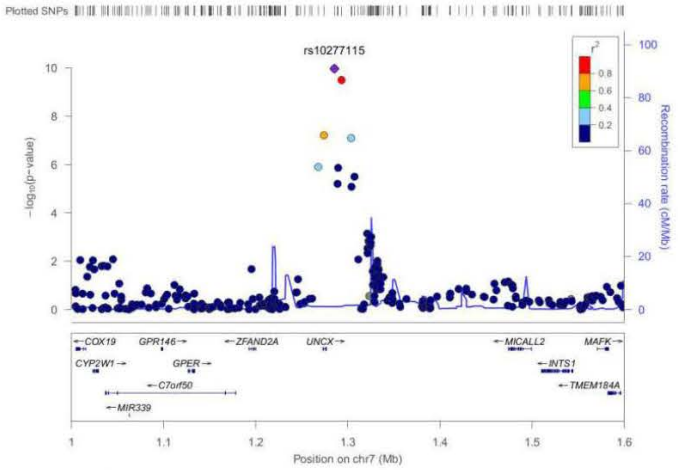
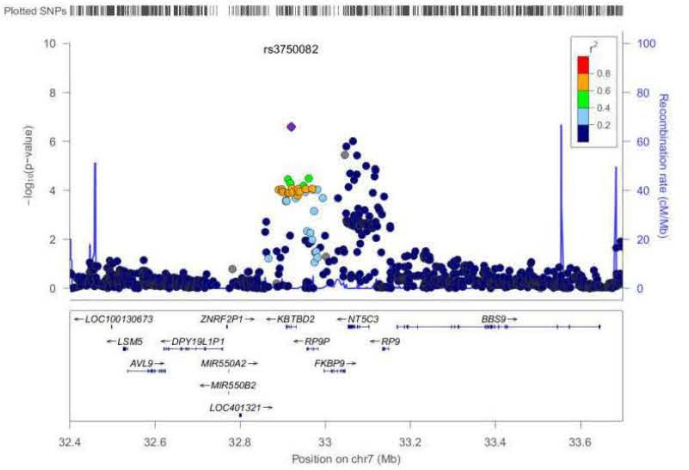
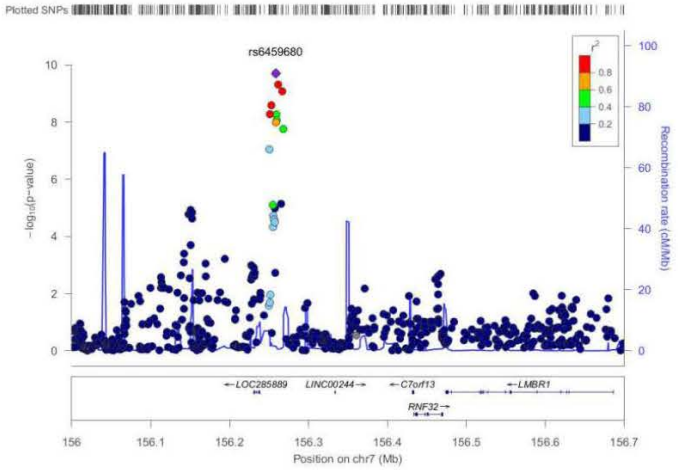
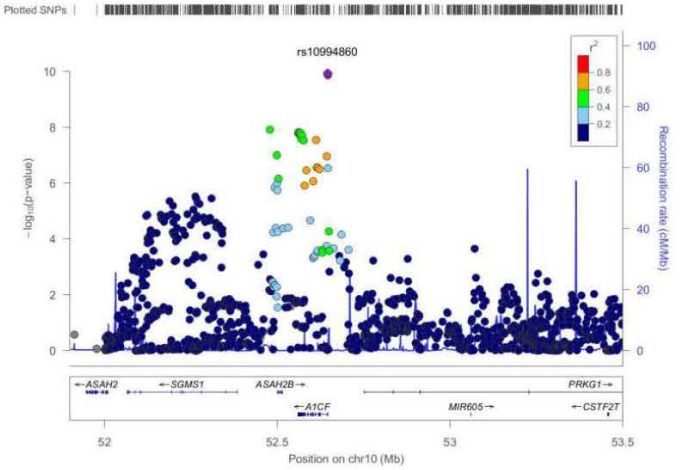
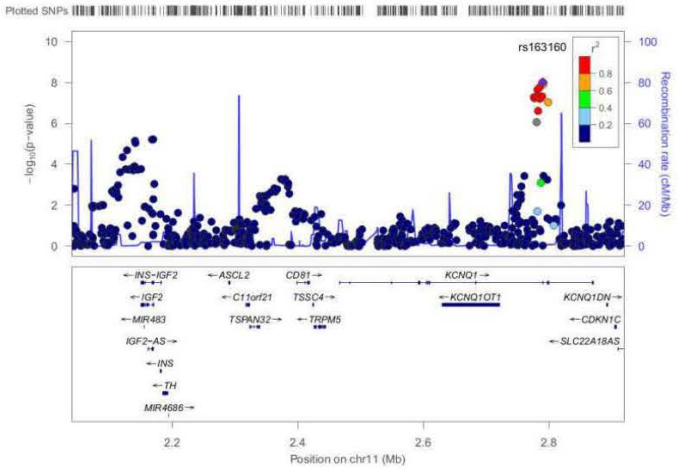
28
Position on chr6 (Mb)

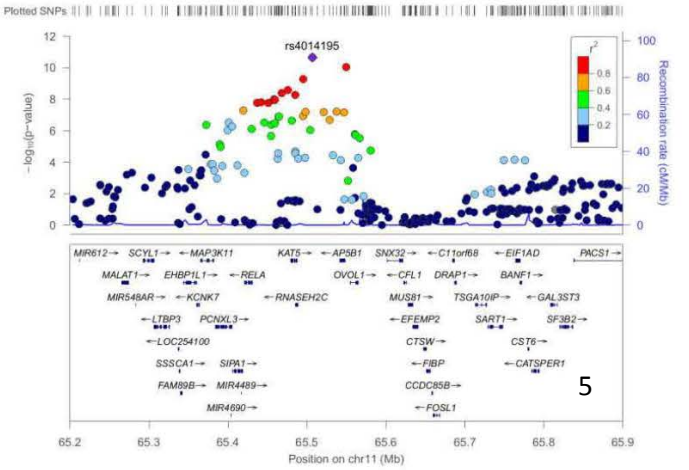

Plotted SNPs
rs10277115
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
COX19
GPR146
ZFAND2A
UNCX
MICALL2
MAFK
CYP2W1
GPER
INTS1
C7orf50
TMEM184A
MIR339
1
1.1
1.2
1.3
1.4
1.5
1.6
Position on chr7 (Mb)

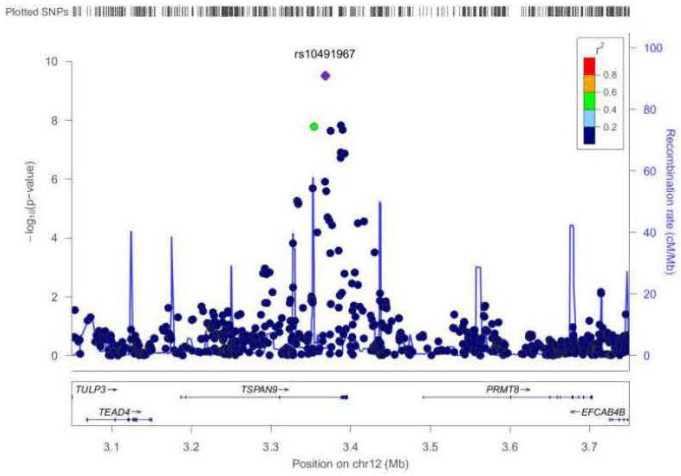

Plotted SNPs
rs3750082
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
LOC100130673
ZNRF2P1
KBTBD2
NT5C3
BBS9
LSM5
DPY19L1P1
RP9P
RP9
AVL9
MIR550A2
FKBP9
MIR550B2
LOC401321
32.4
32.6
32.8
33
33.2
33.4
33.6
Position on chr7 (Mb)

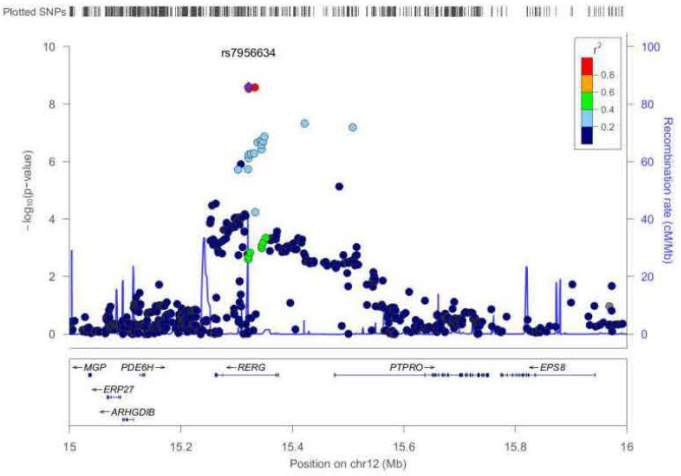

Plotted SNPs
rs6459680
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
LOC285889
LINC00244
C7orf13
LMBR1
RNF32
156
156.1
156.2
156.3
156.4
156.5
156.6
156.7
Position on chr7 (Mb)

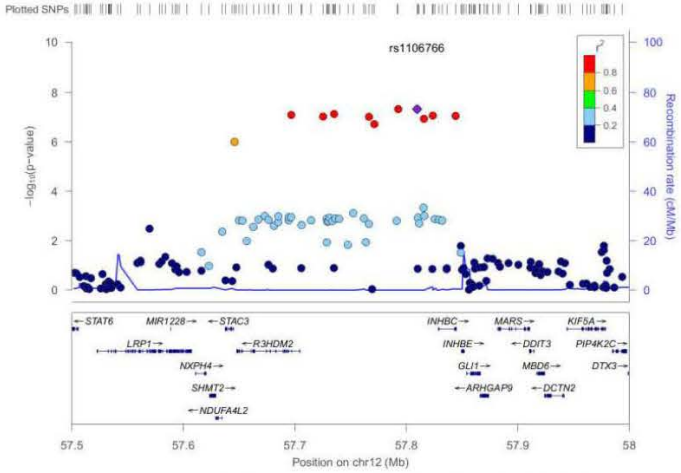

Plotted SNPs
rs10994860
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
ASAH2
SGMS1
ASAH2B
PRKG1
A1CF
MIR605
CSTF2T
52
52.5
53
53.5
Position on chr10 (Mb)

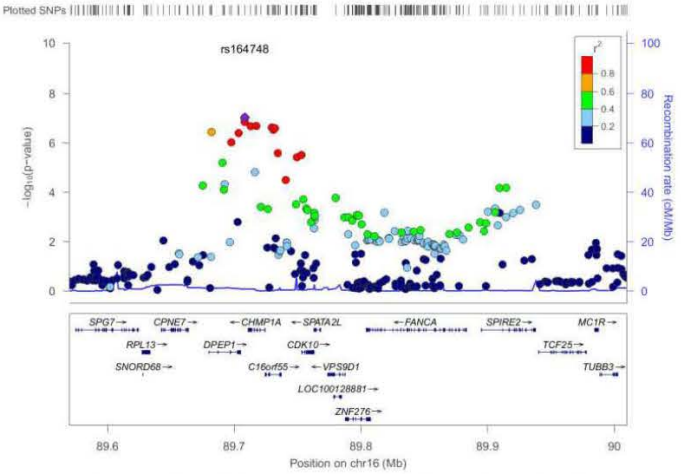

Plotted SNPs
rs163160
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
INS-IGF2
ASCL2
CD81
KCNQ1
IGF2
C11orf21
TSSC4
KCNQ1OT1
KCNQ1DN
MIR483
TSPAN32
TRPM5
CDKN1C
IGF2-AS
SLC22A18AS
INS
TH
MIR4686
2.2
2.4
2.6
2.8
Position on chr11 (Mb)

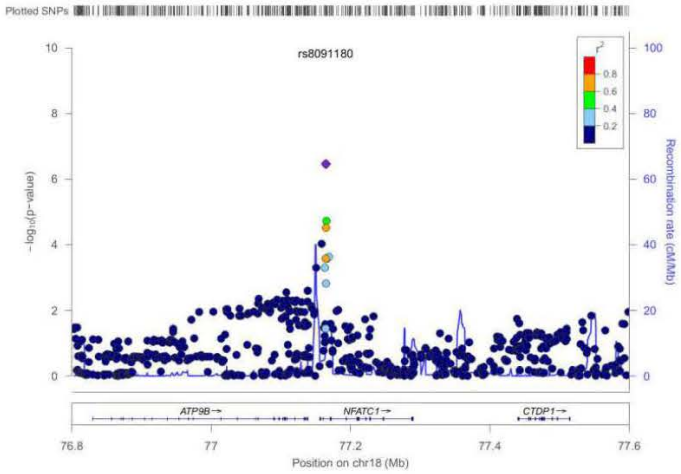

Plotted SNPs
rs4014195
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
MIR612
SCYL1
MAP3K11
KAT5
AP5B1
SNX32
C11orf68
EIF1AD
PACS1
MALAT1
EHBP1L1
RELA
OVOL1
CFL1
DRAP1
BANF1
MIR548AR
KCNK7
RNASEH2C
MUS81
TSGA10IP
GAL3ST3
LTBP3
PCNXL3
EFEMP2
SART1
SF3B2
LOC254100
CTSW
CST6
SSSCA1
SIPA1
FIBP
CATSPER1
FAM89B
MIR4489
CCDC85B
MIR4690
FOSL1
65.2
65.3
65.4
65.5
65.6
65.7
65.8
65.9
Position on chr11 (Mb)

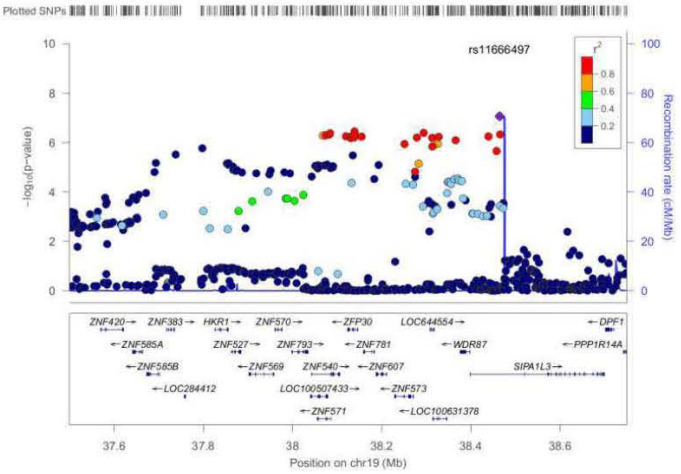

Plotted SNPs
rs10491967
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
TULP3→
TSPAN9→
PRMT8→
TEAD4→
←EFCAB4B
Position on chr12 (Mb)

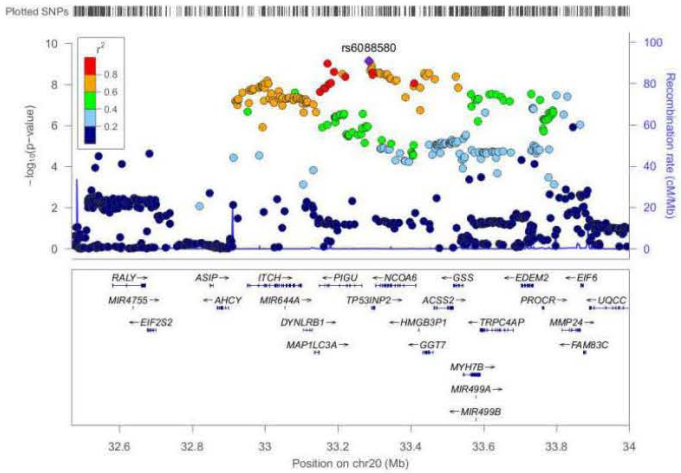

Plotted SNPs
rs7956634
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
←MGP
PDE6H→
←RERG
PTPRO→
←EPS8
←ERP27
←ARHGDIB
Position on chr12 (Mb)

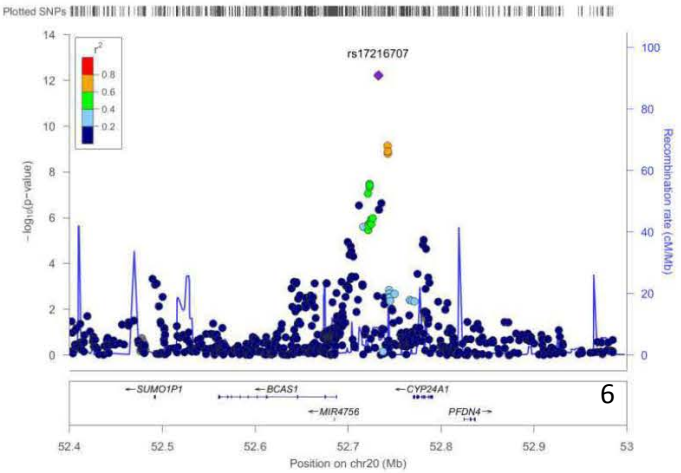

Plotted SNPs
rs1106766
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
←STAT6
MIR1228→
←STAC3
INHBC→
MARS→
KIF5A→
LRP1→
←R3HDM2
INHBE→
←DDIT3
PIP4K2C→
NXPH4→
GLI1→
MBD6→
DTX3→
SHMT2→
←ARHGAP9
←DCTN2
←NDUFA4L2
Position on chr12 (Mb)


Plotted SNPs
rs164748
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
SPG7→
CPNE7→
←CHMP1A
←SPATA2L
←FANCA
SPIRE2→
MC1R→
RPL13→
DPEP1→
CDK10→
TCF25→
SNORD68→
C16orf55→
←VPS9D1
TUBB3→
LOC100128881→
ZNF276→
Position on chr16 (Mb)

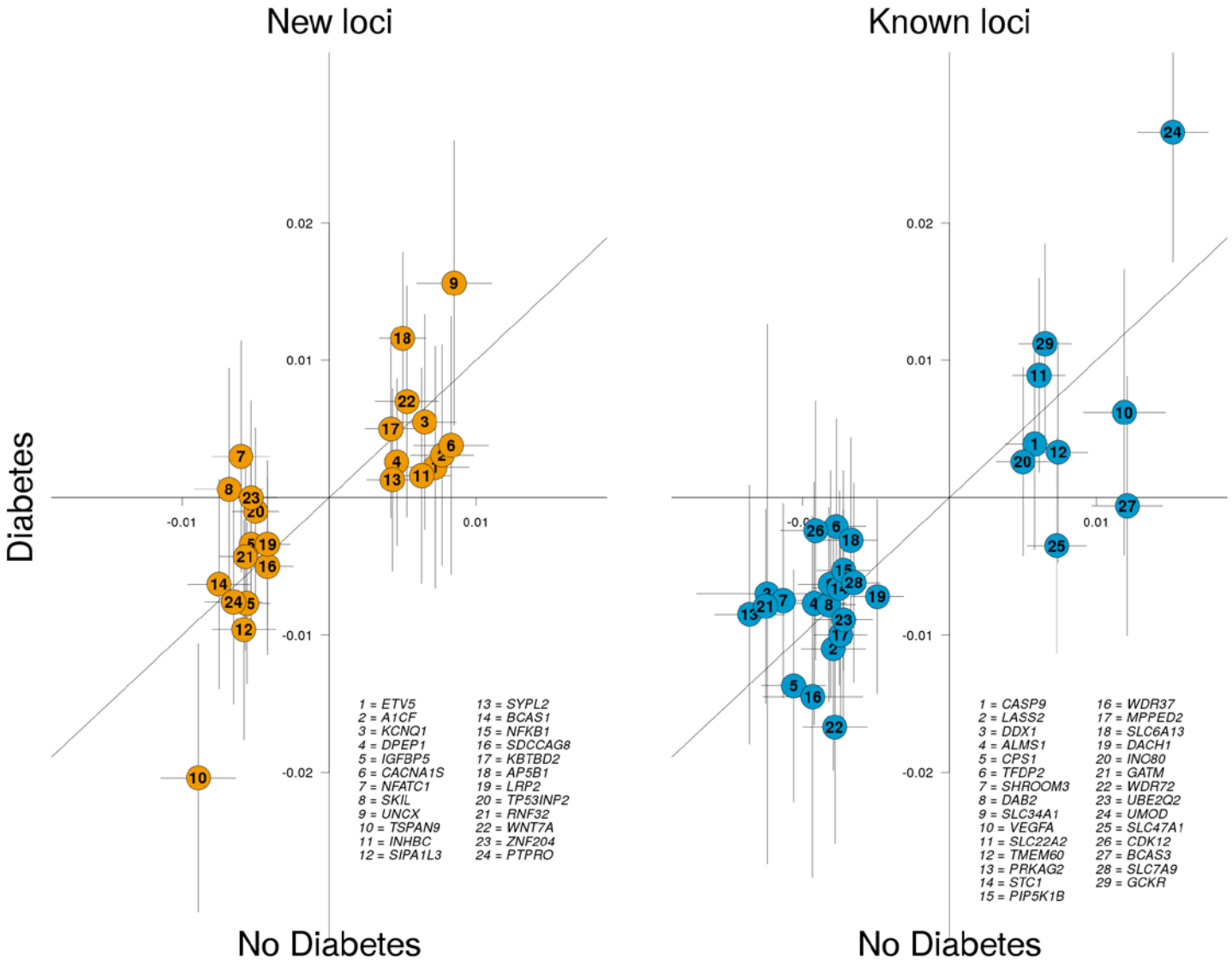

Plotted SNPs
rs8091180
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
ATP9B→
NFATC1→
CTDP1→
Position on chr18 (Mb)


Plotted SNPs
rs11666497
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
ZNF420→
ZNF383→
HKR1→
ZNF570→
←ZFP30
LOC644554→
←DPF1
←ZNF585A
ZNF527→
ZNF793→
←ZNF781
←WDR87
←PPP1R14A
←ZNF585B
←ZNF569
ZNF540→
←ZNF607
SIPA1L3→
←LOC284412
LOC100507433→
←ZNF573
←ZNF571
←LOC100631378
Position on chr19 (Mb)

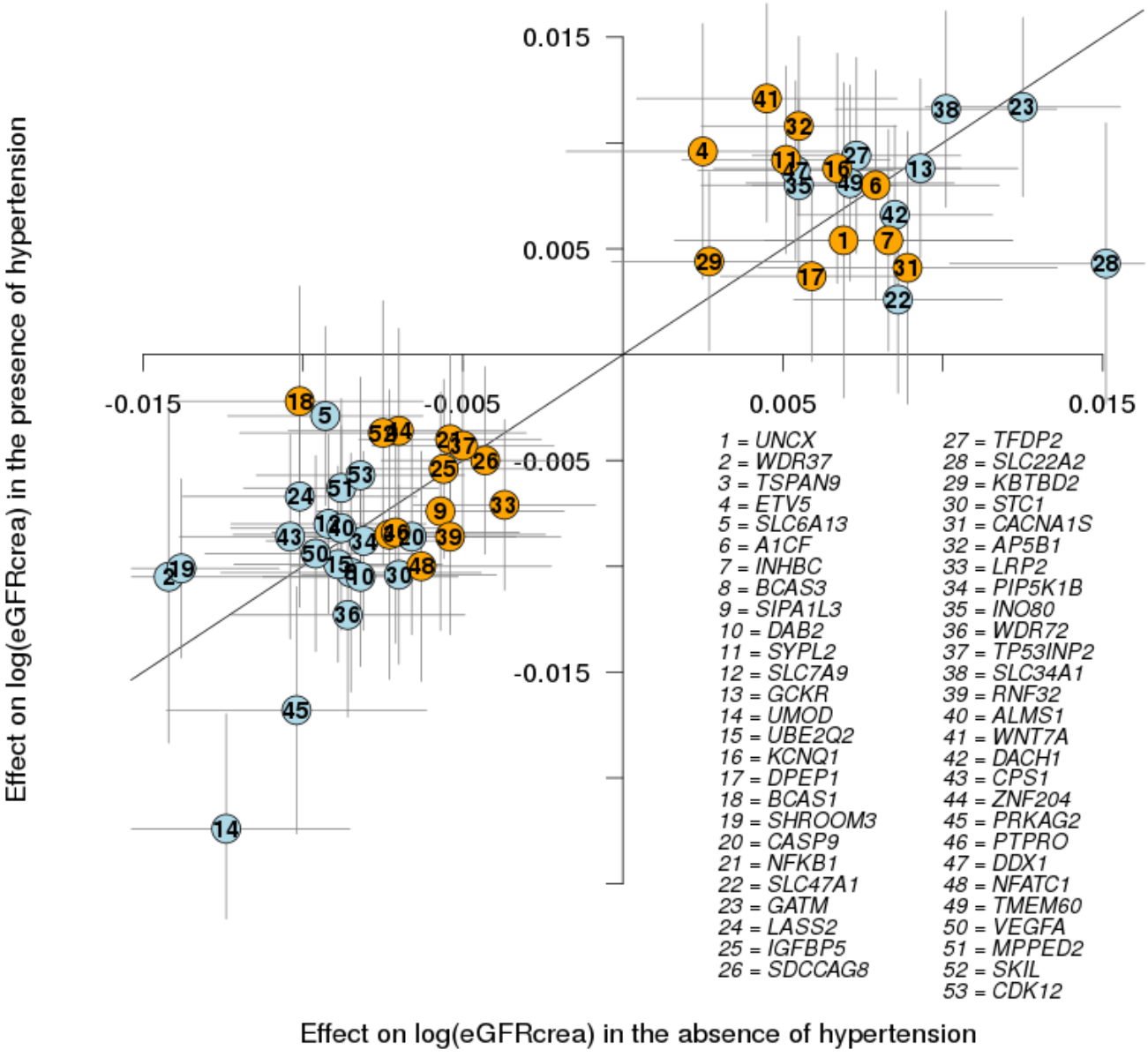

Plotted SNPs
rs6088580
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
RALY→
ASIP→
ITCH→
←PIGU
←NCOA6
←GSS
←EDEM2
←EIF6
MIR4755→
←AHCY
MIR644A→
TP53INP2→
ACSS2→
PROCR→
←UQCC
←EIF2S2
DYNLRB1→
←HMGB3P1
←TRPC4AP
MMP24→
MAP1LC3A→
←GGT7
←FAM83C
MYH7B→
MIR499A→
←MIR499B
Position on chr20 (Mb)


Plotted SNPs
rs17216707
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
$r^2$
0.8
0.6
0.4
0.2
←SUMO1P1
←BCAS1
←CYP24A1
←MIR4756
PFDN4→
Position on chr20 (Mb)

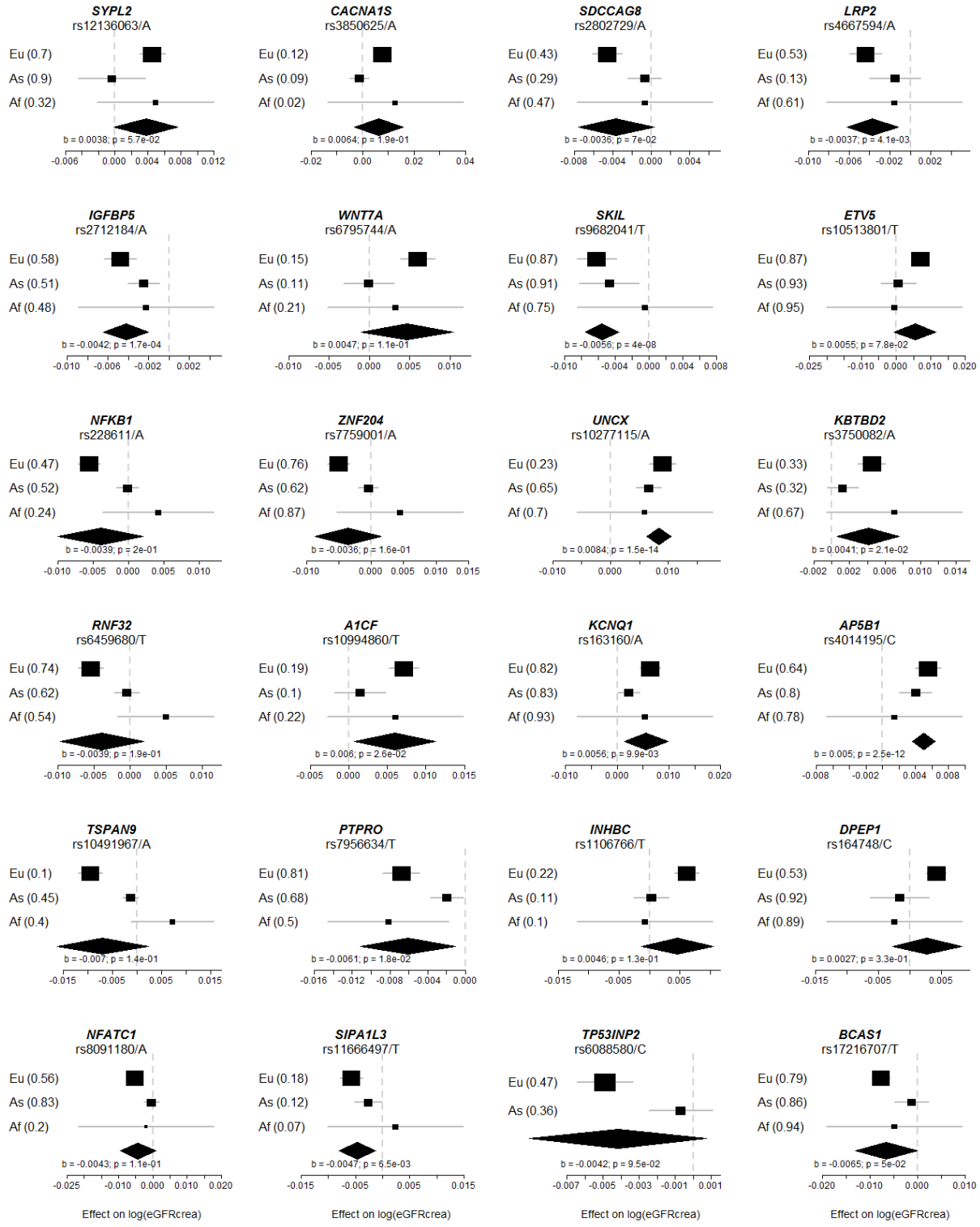
**Supplementary Figure 5**. Effects of known and novel loci on eGFRcrea in individuals with (n=16,477) and without (n=154,881) diabetes. The Pearson's correlation coefficient between the effects in the two groups was 0.80 across all loci (95% confidence interval: 0.67, 0.88). The corresponding correlation coefficient when considering all ~2.5 million genetic variants was of 0.044 (see "Test for differential effects on eGFRcrea between diabetes and hypertension strata", in the Methods), highlighting that most of replicated loci are associated with eGFRcrea regardless of the presence or absence of diabetes.



**Supplementary Figure 6**. Effect of the 53 known (light blue) and new (orange) loci on log(eGFRcrea) in the absence versus presence of hypertension. Data are derived from our previous analysis[3] and based on n = 29,592 and 44,319 hypertensive and non-hypertensive subjects, respectively.



**Supplementary Figure 7.** Forest plots from trans-ethnic random-effect meta-analysis for all 24 novel loci. Indicated are: index SNP and effect allele; ancestry (Eu = European, As = Asian; Af = African) along with effect allele frequencies in parenthesis. Dot sizes are proportional to study sample sizes. Bars indicate 95% confidence intervals. The random-effect estimate is reported as a rhomb and as a number (b) followed by the p-value (p).



**Supplementary Table 1**. Sample characteristics of discovery and replication studies.

| Study[1] | Sample size | | | Women % (N) | Age Mean (SD) | eGFRcrea Mean(SD) ml / min / 1.73m$^2$ | eGFRcys Mean(SD) ml / min / 1.73m$^2$ | CKD % (N) | HTN % (N) | DM % (N) |
|---|---|---|---|---|---|---|---|---|---|---|
| | eGFRcrea | CKD | eGFRcys | | | | | | | |
| **Discovery studies** | | | | | | | | | | |
| **3C** | 6431 | 6431 | 1243 | 60.8 (3911) | 74(5) | 73.1(16.9) | 90.5(22.7) | 20.4 (1311) | 79.0 (6431) | 9.7 (623) |
| **Advance** | 2287 | 2287 | NA | 32.8 (755) | 67(7) | 85.1(29.2) | NA | 14.7 (337) | 47.6 (1096) | 100.0 (2287) |
| **AGES** | 3219 | 3219 | NA | 58.0 (1867) | 76(5) | 73.0(20.0) | NA | 24.2 (781) | 80.6 (2595) | 11.5 (368) |
| **Amish** | 1211 | NA | 783 | 48.9 (592) | 49(17) | 93.7(19.7) | 114.9(18.0) | 3.1 (37) | 18.9 (229) | 1.7 (20) |
| **ARIC** | 8982 | 8982 | 7145 | 53.1 (4767) | 62(6) | 81.4(17.5) | 84.2(19.7) | 8.7 (782) | 40.7 (3643) | 14.2 (1276) |
| **ASPS** | 848 | 848 | NA | 56.8 (482) | 65(8) | 96.5(39.9) | NA | 8.1 (69) | 72.5 (615) | 9.2 (78) |
| **AUSTWIN** | 9592 | 3320 | NA | 60.9 (5846) | 46(13) | 98.3(26.2) | NA | 10.5 (350) | NA | NA |
| **BLSA** | 723 | 723 | NA | 46.1 (333) | 70(15) | 80.3(23.1) | NA | 17.4 (126) | 21.9 (147) | 7.7 (55) |
| **BMES** | 2437 | 2437 | NA | 56.8 (1385) | 69(9) | 78.7(20.2) | NA | 13.2 (322) | 76.4 (1861) | 10.9 (265) |
| **CHS** | 2820 | 2353 | 2475 | 61.3 (1729) | 72(5) | 77.3(20.8) | 81.0(17.9) | 9.5 (224) | 51.4 (1441) | 11.0 (307) |
| **CROATIA-KORCULA** | 888 | 888 | NA | 64.0 (568) | 56(14) | 87.3(20.6) | NA | 7.5 (67) | 54.2 (474) | 13.1 (116) |
| **CROATIA-SPLIT** | 478 | 478 | NA | 59.8 (286) | 49(15) | 104.8(23.8) | NA | 5.0 (24) | 39.4 (186) | 5.0 (24) |
| **CROATIA-VIS** | 768 | 768 | NA | 58.6 (450) | 57(15) | 88.2(22.1) | NA | 6.9 (53) | 52.2 (396) | 12.0 (91) |
| **DESIR** | 715 | NA | NA | 75.2 (550) | 50(8) | 92.0(16.9) | NA | 0.7 (5) | NA | 0.0 (0) |
| **EGCUT 370K** | 863 | NA | NA | 51.2 (442) | 37(16) | 101.5(20.3) | NA | 1.7 (15) | 18.7 (161) | 2.2 (19) |
| **EGCUT Omni** | 261 | 261 | NA | 73.4 (193) | 81(9) | 71.2(24.1) | NA | 34.2 (90) | 82.5 (217) | 21.8 (57) |
| **ERF** | 2561 | 2561 | NA | 55.3 (1416) | 49(14) | 93.3(21.4) | NA | 3.7 (96) | 52.9 (1355) | 6.1 (155) |
| **FamHS** | 3838 | 3838 | 521 | 52.4 (2012) | 52(14) | 91.6(20.1) | 86.3(33.5) | 4.2 (161) | 25.5 (979) | 7.7 (291) |
| **FHS** | 7782 | 4142 | 3002 | 54.3 (4229) | 51(14) | 92.1(21.7) | 83.8(17.8) | 10.7 (445) | 57.5 (2390) | 9.7 (405) |
| **GENOA** | 1163 | 1163 | NA | 56.3 (655) | 59(10) | 87.7(24.0) | NA | 10.7 (125) | 73.3 (852) | 15.3 (178) |
| **HABC** | 1663 | 1663 | 1663 | 47.1 (784) | 74(3) | 71.2(14.8) | 77.0(19.9) | 25.0 (415) | 63.7 (1060) | 13.0 (216) |
| **HCS** | 1235 | 1235 | NA | 49.6 (630) | 66(7) | 79.9(18.1) | NA | 11.3 (144) | 45 (544) | 10.5 (127) |
| **HPFS** | 818 | 818 | NA | 0.0 (0) | 65(8) | 85.2(22.7) | NA | 9.5 (78) | 59 (479) | 100.0 (818) |
| **HYPERGENES HTN cases** | 1591 | 1591 | NA | 33.0 (525) | 48(10) | 94.5(23.1) | NA | 3.7 (59) | 100.0 (1591) | 0.0 (0) |
| **HYPERGENES HTN ctrls** | 1662 | 1662 | NA | 39.6 (659) | 60(10) | 87.8(19.0) | NA | 4.9 (81) | 0.0 (0) | 0.0 (0) |
| **INCIPE** | 940 | 940 | 875 | 52.7 (495) | 61(11) | 82.6(18.5) | 88.5(22.1) | 8.6 (81) | 69.6 (654) | 10.6 (100) |

**Supplementary Table 1** (continued)**.**

| Study[1] | Sample size | | | Women % (N) | Age Mean (SD) | eGFRcrea Mean(SD) ml / min / 1.73m$^2$ | eGFRcys Mean(SD) ml / min / 1.73m$^2$ | CKD % (N) | HTN % (N) | DM % (N) |
|---|---|---|---|---|---|---|---|---|---|---|
| | eGFRcrea | CKD | eGFRcys | | | | | | | |
| **Discovery studies** | | | | | | | | | | |
| **INGI-CARLANTINO** | 447 | NA | NA | 60.8 (272) | 50(16) | 93.9(22.4) | NA | NA | 34.9 (156) | 9.4 (42) |
| **INGI-CILENTO** | 821 | 821 | NA | 54.9 (451) | 54(18) | 88.7(21.8) | NA | 8.0 (66) | 38.4 (315) | 10.5 (86) |
| **INGI-FVG** | 874 | 874 | NA | 59.4 (519) | 52(16) | 90.6(21.8) | NA | 6.0 (52) | 48.8 (427) | 6.7 (59) |
| **INGI-VAL BORBERA** | 1636 | 1636 | NA | 55.8 (913) | 55(18) | 89.2(23.3) | NA | 8.5 (139) | 43.8 (717) | 6.5 (107) |
| **JUPITER** | 8780 | 8780 | NA | 32.2 (2827) | 66(8) | 80.1(18.1) | NA | 11.5 (1008) | 55.8 (4901) | 0.4 (37) |
| **KORA-F3** | 1641 | 1641 | 1642 | 50.5 (831) | 62(10) | 83.9(21.0) | 111.8(26.3) | 10.8 (177) | 41.1 (674) | 11.1 (179) |
| **KORA-F4** | 1814 | 1814 | 1811 | 51.3 (930) | 61(9) | 85.1(20.2) | 109.7(26.2) | 7.0 (127) | 20.9 (379) | 9.2 (167) |
| **MESA** | 2521 | 2521 | 2521 | 52.0 (1311) | 63(10) | 82.4(18.3) | 90.0(21.7) | 9.7 (245) | 38.6 (974) | 6.0 (151) |
| **MICROS** | 1201 | 1201 | 1198 | 56.5 (678) | 46(16) | 94.6(20.9) | 107.4(23.8) | 3.8 (46) | 37.7 (437) | 4.3 (49) |
| **NESDA** | 1856 | NA | 1856 | 67.5 (1253) | 42(12) | 98.4(20.7) | 112.4(24.9) | 1.1 (20) | 30.3 (563) | 5.1 (95) |
| **NHS** | 786 | 786 | NA | 100.0 (786) | 59(6) | 86.2(22.1) | NA | 10.7 (84) | 70 (554) | 100.0 (786) |
| **NSPHS** | 565 | 565 | NA | 53.1 (300) | 52(18) | 91.0(22.1) | NA | 5.7 (32) | 43.4 (242) | 7.8 (44) |
| **OGP-TALANA** | 862 | 862 | NA | 57.3 (494) | 51(19) | 91.2(23.6) | NA | 7.5 (65) | 37.3 (322) | 5.1 (44) |
| **ORCADES** | 704 | 704 | NA | 53.6 (377) | 54(15) | 89.4(20.7) | NA | 6.8 (48) | 41.8 (287) | 4.0 (28) |
| **POPGEN** | 1163 | 1163 | NA | 44.4 (516) | 55(14) | 88.1(18.8) | NA | 5.1 (59) | 46.8 (541) | 3.8 (44) |
| **PREVEND** | NA | NA | 1885 | 48.9 (923) | 50(12) | NA | 105.4(25.3) | NA | 33.5 (631) | 3.7 (70) |
| **PROSPER-PHASE** | 5236 | 5236 | NA | 51.7 (2718) | 75(3) | 72.0(21.4) | NA | 29.6 (1549) | 62.1 (3251) | 10.4 (544) |
| **RS-I** | 4390 | 4390 | NA | 61.4 (2696) | 70(9) | 77.1(17.2) | NA | 13.7 (600) | 34.1 (1497) | 10.7 (470) |
| **RS-II** | 1863 | 1863 | NA | 54.5 (1015) | 65(8) | 81.3(17.2) | NA | 9.1 (169) | 28.4 (530) | 11.1 (207) |
| **SAPALDIA** | 1444 | 1444 | NA | 51.0 (737) | 52(11) | 90.3(17.3) | NA | 3.1 (44) | 27.4 (389) | 2.8 (40) |
| **SHIP** | 3228 | 3228 | 3228 | 51.7 (1670) | 54(15) | 90.4(23.6) | 97.1(25.3) | 7.7 (248) | 51.1 (1649) | 11.2 (362) |
| **SHIP-TREND** | 986 | 986 | 986 | 56.2 (554) | 50(14) | 92.4(22.1) | 122.1(22.1) | 4.3 (42) | 39.6 (390) | 1.8 (18) |
| **SORBS** | 856 | 856 | NA | 58.5 (501) | 49(16) | 92.2(19.0) | NA | 4.1 (35) | 53.2 (455) | 9.3 (80) |
| **WGHS** | 21940 | 23186 | NA | 100.0 (21,940) | 55(7) | 90.0(22.5) | NA | 6.1 (1329) | 24.5 (5374) | 2.5 (554) |
| **YFS** | 2023 | NA | NA | 54.7 (1107) | 38(5) | 100.3(15.8) | NA | 0.2 (5) | 20.0 (404) | 1.9 (39) |

**Supplementary Table 1** (continued).

| Study[1] | Sample size | | | Women % (N) | Age Mean (SD) | eGFRcrea Mean(SD) ml / min / 1.73m$^2$ | eGFRcys Mean(SD) ml / min / 1.73m$^2$ | CKD % (N) | HTN % (N) | DM % (N) |
|---|---|---|---|---|---|---|---|---|---|---|
| | eGFRcrea | CKD | eGFRcys | | | | | | | |
| **Replication studies** | | | | | | | | | | |
| **Bus Santé** | 4408 | 4408 | NA | 49.4 (2178) | 58(11) | 85.6(15.6) | NA | 4.3 (186) | 28.3 (1249) | 7.4 (327) |
| **EGCUT_replic** | 1519 | 1519 | 1037 | 46.2 (703) | 58(17) | 97.4(29.3) | 85.5(16.9) | 8.8 (134) | 59.5 (905) | 6.3 (97) |
| **ESTHER** | 3604 | 3604 | NA | 55.6 (2004) | 62(7) | 90.3(34.4) | NA | 15.7 (565) | 57.5 (2073) | 15.9 (572) |
| **GENDIAN** | 450 | 450 | 450 | 47.1 (212) | 65(10) | 69.1(20.2) | 85.3(27.1) | 32.3 (145) | 53.0 (237) | 100.0 (450) |
| **GHS 1** | 2995 | 2995 | NA | 48.5 (1452) | 56(11) | 87.3(16.5) | NA | 3.7 (112) | 52.6 (1575) | 7.2 (215) |
| **GHS 2** | 1179 | 1179 | NA | 50.0 (590) | 55(11) | 86.7(16.2) | NA | 4.5 (53) | 48.4 (570) | 7.6 (90) |
| **GSK** | 1721 | 1721 | NA | 66.6 (1147) | 51(13) | 92.3(22.6) | NA | 5.5 (95) | 43.7 (752) | 4.6 (80) |
| **HRS** | NA | NA | 7700 | 58.9 (4537) | 68(10) | NA | 102.5(20.3) | 2.9 (221) | 66.1 (5087) | 20.5 (1557) |
| **KORA-F3 non-GWAS** | 1494 | NA | 1493 | 52.5 (787) | 52(13) | 92.6(21.3) | 123.5(29.1) | 2.6 (39) | 29.4 (437) | 5.1 (76) |
| **KORA-F4 non-GWAS** | 1199 | 1200 | 1196 | 52.4 (629) | 49(15) | 92.6(22.4) | 118.4(27.5) | 5.8 (70) | 13.3 (159) | 4.0 (48) |
| **IPM_EA_Affy** | 440 | NA | NA | 30.2 (133) | 62(13) | 94.8(36.8) | NA | 19.1 (84) | 60.5 (266) | 26.0 (99) |
| **IPM_EA_Illu** | 1307 | 1307 | NA | 48.6 (635) | 68(9) | 86.1(27.8) | NA | 14.8 (194) | 55.1 (720) | 15.0 (185) |
| **LURIC** | 3056 | 3056 | 3054 | 30.0 (917) | 63(11) | 86.0(21.7) | 84.7(22.6) | 10.0 (305) | 72.7 (2223) | 32.6 (996) |
| **OGP** | 9554 | 5884 | NA | 56.9 (5440) | 50(17) | 98.6(35.0) | NA | 8.1 (776) | 36.0 (3443) | 6.2 (596) |
| **SAPHIR** | 1721 | NA | NA | 37.1 (639) | 51(6) | 91.7(16.1) | NA | 6.9 (19) | 55.7 (959) | 3.3 (56) |
| **SKIPOGH** | 870 | NA | NA | 52.3 (455) | 47(18) | 94.2(24.6) | NA | 5.7 (50) | 22.9 (198) | 4.5 (39) |
| **Vanderbilt Omni1** | 3221 | 3221 | NA | 47.3 (1525) | 54(19) | 80.0(36.9) | NA | 27.7 (891) | 70.5 (2271) | 18.0 (581) |
| **Vanderbilt Omni5** | 1129 | 1129 | NA | 46.9 (529) | 50(21) | 89.0(44.4) | NA | 21.7 (245) | 58.2 (657) | 33.3 (376) |
| **Vanderbilt 660W** | 2299 | 2299 | NA | 56.5 (1298) | 56(17) | 78.6(23.9) | NA | 20.6 (474) | 57.2 (1316) | 17.9 (411) |

[1] Extended study names are given in the Acknowledgements section.

**Supplementary Table 2**. Association of previously identified loci. For each locus, we report the best SNP from the current discovery GWAS (current best SNP). The previously reported best SNP is reported for comparison.

| ID of current best SNP in the locus | Chr | Position (Build 37) | Locus name* | Ref. / Non-Ref. All. (Ref All Freq) | eGFRcrea | | CKD | | Previously reported SNP in the locus | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | beta(SE)† | P-value† | Odds Ratio (95%CI) † | P-value† | ID of previously reported SNP[REF] | LD[#] with current best SNP $r^2$/D' | P-value in current GWAS† |
| rs1800615 | 1 | 15,832,281 | *CASP9* | T/C(0.30) | -0.0058(0.0009) | 1.90E-09 | 1.04 (1.00,1.07) | 3.40E-02 | rs12124078[3] | 1.00/1.00 | 3.09E-09 |
| rs267734 | 1 | 150,951,477 | *LASS2* | T/C(0.79) | -0.0079(0.0011) | 4.01E-13 | 1.06 (1.02,1.10) | 3.52E-03 | same[4] | | |
| rs807601 | 2 | 15,793,014 | *DDX1* | T/G(0.34) | 0.0064(0.0009) | 6.60E-12 | 0.99 (0.96,1.02) | 5.28E-01 | rs6431731[3] | 0.04/0.60 | 2.95E-07 |
| rs1260326 | 2 | 27,730,940 | *GCKR* | T/C(0.42) | 0.0068(0.0009) | 3.38E-14 | 0.98 (0.95,1.01) | 1.36E-01 | same[4] | | |
| rs6546838 | 2 | 73,679,280 | *ALMS1* | A/G(0.76) | -0.0093(0.0010) | 7.72E-20 | 1.05 (1.02,1.09) | 4.63E-03 | rs13538[4] | 0.95/1.00 | 3.15E-17 |
| rs7422339 | 2 | 211,540,507 | *CPS1* | A/C(0.32) | -0.0106(0.0010) | 2.18E-23 | 1.11 (1.07,1.15) | 7.54E-09 | same[5] | | |
| rs2861422 | 3 | 141,724,644 | *TFDP2* | T/C(0.27) | 0.0074(0.0010) | 9.12E-14 | 0.96 (0.92,0.99) | 7.59E-03 | rs347685[4] | 0.96/1.00 | 1.87E-13 |
| rs17319721 | 4 | 77,368,847 | *SHROOM3* | A/G(0.43) | -0.0114(0.0009) | 1.32E-37 | 1.07 (1.04,1.10) | 7.71E-06 | same[5] | | |
| rs11959928 | 5 | 39,397,132 | *DAB2* | A/T(0.44) | -0.0083(0.0009) | 1.66E-20 | 1.06 (1.02,1.09) | 4.20E-04 | same[4] | | |
| rs6420094 | 5 | 176,817,636 | *SLC34A1* | A/G(0.66) | 0.0096(0.0010) | 4.92E-22 | 0.91 (0.88,0.94) | 3.68E-09 | same[4] | | |
| rs9472135 | 6 | 43,809,802 | *VEGFA* | T/C(0.71) | -0.0080(0.0010) | 3.34E-15 | 1.07 (1.04,1.11) | 3.37E-05 | rs881858[4] | 0.88/0.96 | 7.51E-15 |
| rs316009 | 6 | 160,675,764 | *SLC22A2* | T/C(0.10) | 0.0131(0.0014) | 4.38E-19 | 0.96 (0.91,1.01) | 9.71E-02 | rs2279463[4] | 0.01/1.00 | 2.94E-16 |
| rs848490 | 7 | 77,555,005 | *TMEM60* | C/G(0.73) | 0.0073(0.0010) | 7.80E-13 | 0.93 (0.90,0.97) | 1.44E-04 | rs6465825[4] | 0.41/1.00 | 4.91E-12 |
| rs7805747 | 7 | 151,407,801 | *PRKAG2* | A/G(0.25) | -0.0130(0.0011) | 7.96E-29 | 1.16 (1.11,1.20) | 2.06E-14 | same[4] | | |
| rs3758086 | 8 | 23,714,992 | *STC1* | A/G(0.42) | -0.0071(0.0009) | 1.71E-15 | 1.06 (1.02,1.09) | 4.13E-04 | rs10109414[5] | 1.00/1.00 | 2.31E-15 |
| rs4744712 | 9 | 71,434,707 | *PIP5K1B* | A/C(0.40) | -0.0071(0.0009) | 4.29E-15 | 1.06 (1.03,1.09) | 7.59E-05 | same[4] | | |
| rs1044261 | 10 | 1,065,710 | *WDR37* | T/C(0.08) | -0.0113(0.0016) | 1.21E-11 | 1.15 (1.09,1.22) | 3.62E-07 | rs10794720[4] | 0.42/0.69 | 3.23E-09 |
| rs963837 | 11 | 30,749,090 | *MPPED2* | T/C(0.54) | -0.0078(0.0009) | 5.69E-18 | 1.09 (1.05,1.12) | 9.03E-08 | rs3925584[3] | 0.93/0.97 | 7.58E-18 |
| rs10774021 | 12 | 349,298 | *SLC6A13* | T/C(0.65) | -0.0063(0.0009) | 4.77E-12 | 1.04 (1.01,1.07) | 1.17E-02 | same[4] | | |
| rs716877 | 13 | 72,347,448 | *DACH1* | C/G(0.40) | 0.0049(0.0009) | 6.22E-08 | 0.97 (0.94,1.00) | 3.15E-02 | rs626277[4] | 1.00/1.00 | 7.98E-08 |
| rs476633 | 15 | 41,392,134 | *INO80* | C/G(0.57) | 0.0051(0.0009) | 8.90E-09 | 0.94 (0.91,0.97) | 2.84E-05 | rs2928148[3] | 0.84/1.00 | 1.28E-07 |
| rs2467853 | 15 | 45,698,793 | *GATM* | T/G(0.62) | 0.0126(0.0009) | 1.05E-42 | 0.90 (0.87,0.93) | 1.88E-11 | rs2453533[5] | 1.00/1.00 | 4.26E-42 |
| rs491567 | 15 | 53,946,593 | *WDR72* | A/C(0.78) | -0.0084(0.0010) | 2.86E-15 | 1.08 (1.04,1.12) | 7.48E-05 | same[4] | | |
| rs1394125 | 15 | 76,158,983 | *UBE2Q2* | A/G(0.35) | -0.0073(0.0010) | 5.47E-14 | 1.07 (1.04,1.11) | 3.02E-05 | same[4] | | |
| rs13329952 | 16 | 20,366,507 | *UMOD* | T/C(0.81) | -0.0158(0.0011) | 9.47E-43 | 1.24 (1.19,1.29) | 1.98E-25 | rs12917707[5] | 0.95/1.00 | 1.16E-41 |
| rs2453580 | 17 | 19,438,321 | *SLC47A1* | T/C(0.59) | 0.0064(0.0009) | 2.93E-11 | 0.94 (0.91,0.97) | 2.60E-04 | same[3] | | |
| rs9916302 | 17 | 37,499,949 | *CDK12 / FBXL20* | T/C(0.74) | -0.008(0.0010) | 4.78E-15 | 1.03 (0.99,1.07) | 9.43E-02 | rs7208487[3]<br>rs11078903[6] | 0.49/1.00<br>0.87/1.00 | 1.53E-12<br>5.09E-13 |
| rs11657044 | 17 | 59,450,105 | *BCAS3* | T/C(0.19) | -0.0115(0.0012) | 7.89E-22 | 1.06 (1.02,1.10) | 6.56E-03 | rs9895661[4] | 0.94/1.00 | 2.76E-21 |
| rs12460876 | 19 | 33,356,891 | *SLC7A9* | T/C(0.60) | -0.0066(0.0009) | 1.86E-13 | 1.05 (1.02,1.08) | 2.19E-03 | same[4] | | |

*Based on previously reported index gene to facilitate comparison.

†Beta is the effect on log(eGFRcrea in ml/min/1.73 $m^2$); all reported standard errors, confidence intervals, and P-values, are based on the twice-GC corrected results from discovery GWAS meta-analysis.

#LD lookup is based on HapMap 22 CEU obtained using SNAP[7] version 2.2.

**Supplementary Table 3**. All SNPs tested for replication.

| SNPID Locus name* | Chr | Position (bp) (Build 37) | Eff./ Non Eff All (EAF)# | STAGE 1 (discovery)† | | | STAGE 2 (replication)‡ | | | | Combined analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Beta (SE) | P-value | N | Beta (SE) | 1-sided P-value | q-value | N | Beta (SE) | P-value | $I^2$ (%) | Power | Median Rsq |
| **eGFRcrea in the non-diabetes group** | | | | | | | | | | | | | | | | |
| rs3850625 *CACNA1S* | 1 | 201,016,296 | A/G(0.12) | 116,689 | 0.0086 (0.0014) | 2.55E-09 | 36,418 | 0.0071 (0.0028) | 5.10E-03 | 5.46E-03 | 153,107 | 0.0083 (0.0013) | 6.82E-11 | 0 | 0.997 | 1.00 |
| rs2712184 *IGFBP5* | 2 | 217,682,779 | A/C(0.58) | 118,440 | -0.0052 (0.0009) | 1.65E-08 | 35,414 | -0.0055 (0.0018) | 1.20E-03 | 2.06E-03 | 153,854 | -0.0053 (0.0008) | 1.33E-10 | 0 | 0.983 | 1.00 |
| rs9682041 *SKIL* | 3 | 170,091,902 | T/C(0.87) | 118,454 | -0.0072 (0.0013) | 1.36E-07 | 32,457 | -0.0046 (0.0031) | 6.81E-02 | 2.33E-02 | 150,911 | -0.0068 (0.0012) | 2.58E-08 | 2 | 0.948 | 1.00 |
| rs10513801 *ETV5* | 3 | 185,822,353 | T/G(0.87) | 118,374 | 0.0079 (0.0013) | 3.80E-09 | 36,400 | 0.0046 (0.0026) | 3.96E-02 | 1.79E-02 | 154,774 | 0.0072 (0.0012) | 1.03E-09 | 0 | 0.992 | 1.00 |
| rs10994860 *A1CF* | 10 | 52,645,424 | T/C(0.18) | 118,358 | 0.0082 (0.0012) | 1.00E-11 | 36,286 | 0.0061 (0.0024) | 5.10E-03 | 5.46E-03 | 154,644 | 0.0077 (0.0011) | 1.07E-12 | 2 | 0.999 | 0.93 |
| rs163160 *KCNQ1* | 11 | 2,789,955 | A/G(0.82) | 118,373 | 0.0069 (0.0012) | 9.02E-09 | 36,311 | 0.0050 (0.0023) | 1.62E-02 | 9.89E-03 | 154,684 | 0.0065 (0.0011) | 2.26E-09 | 14 | 0.992 | 0.98 |
| rs164748 *DPEP1* | 16 | 89,708,292 | C/G(0.53) | 118,373 | 0.0053 (0.0009) | 9.92E-09 | 36,124 | 0.0019 (0.0018) | 1.42E-01 | 4.19E-02 | 154,497 | 0.0046 (0.0008) | 1.95E-08 | 17 | 0.991 | 0.99 |
| rs8091180 *NFATC1* | 18 | 77,164,243 | A/G(0.56) | 117,447 | -0.0062 (0.0011) | 1.43E-08 | 36,268 | -0.0052 (0.0020) | 5.10E-03 | 5.46E-03 | 153,715 | -0.0060 (0.0010) | 1.28E-09 | 0 | 0.999 | 0.81 |
| rs437065 *ADAMTS5* | 21 | 28,527,399 | C/G(0.14) | 118,358 | 0.0066 (0.0013) | 8.64E-07 | 35,562 | -0.0026 (0.0026) | 1.63E-01 | 4.62E-02 | 153,920 | 0.0047 (0.0012) | 6.78E-05 | 0 | 0.904 | 0.99 |
| **eGFRcrea in the overall sample** | | | | | | | | | | | | | | | | |
| rs12136063 *SYPL2* | 1 | 110,014,170 | A/G(0.70) | 133,723 | 0.0049 (0.0009) | 2.33E-07 | 41,703 | 0.0028 (0.0019) | 6.48E-02 | 2.31E-02 | 175,426 | 0.0045 (0.0008) | 4.71E-08 | 0 | 0.922 | 1.00 |
| rs2802729 *SDCCAG8* | 1 | 243,501,763 | A/C(0.44) | 133,608 | -0.0050 (0.0009) | 7.37E-08 | 41,200 | -0.0029 (0.0018) | 5.02E-02 | 2.05E-02 | 174,808 | -0.0046 (0.0008) | 2.20E-08 | 9 | 0.983 | 0.88 |
| rs2888875 *THADA* | 2 | 43,788,092 | A/G(0.69) | 129,114 | 0.0048 (0.0009) | 7.75E-07 | 41,571 | 0.0012 (0.0018) | 2.60E-01 | 5.72E-02 | 170,685 | 0.0041 (0.0008) | 6.92E-07 | 0 | 0.894 | 0.99 |
| rs17050272 *GLI2* | 2 | 121,306,440 | A/G(0.43) | 132,764 | -0.0048 (0.0009) | 6.63E-07 | 41,681 | -0.0024 (0.0018) | 8.88E-02 | 2.93E-02 | 174,445 | -0.0043 (0.0008) | 1.36E-07 | 19 | 0.964 | 0.90 |
| rs3820716 *ACVR2A* | 2 | 148,680,260 | A/G(0.53) | 133,751 | -0.0052 (0.0009) | 2.73E-09 | 41,642 | 0.0006 (0.0017) | 6.36E-01 | 1.22E-01 | 175,393 | -0.0039 (0.0008) | 1.36E-06 | 17 | 0.994 | 1.00 |
| rs4667594 *LRP2* | 2 | 170,008,506 | A/T(0.53) | 133,715 | -0.0045 (0.0009) | 2.37E-07 | 41,622 | -0.0043 (0.0017) | 5.90E-03 | 5.62E-03 | 175,337 | -0.0044 (0.0008) | 3.52E-08 | 4 | 0.922 | 1.00 |
| rs6795744 *WNT7A* | 3 | 13,906,850 | A/G(0.15) | 133,718 | 0.0071 (0.0012) | 9.60E-09 | 41,772 | 0.0019 (0.0024) | 2.10E-01 | 5.15E-02 | 175,490 | 0.0060 (0.0011) | 3.33E-08 | 18 | 0.990 | 0.98 |

**Supplementary Table 3** (continued).

| SNPID Locus name* | Chr | Position (bp) (Build 37) | Eff./ Non Eff All (EAF)# | STAGE 1 (discovery)† | | | STAGE 2 (replication)‡ | | | | Combined analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Beta (SE) | P-value | N | Beta (SE) | 1-sided P-value | q-value | N | Beta (SE) | P-value | $I^2$ (%) | Power | Median Rsq |
| **eGFRcrea in the overall sample** | | | | | | | | | | | | | | | | |
| rs6795744 *WNT7A* | 3 | 13,906,850 | A/G(0.15) | 133,718 | 0.0071 (0.0012) | 9.60E-09 | 41,772 | 0.0019 (0.0024) | 2.10E-01 | 5.15E-02 | 175,490 | 0.0060 (0.0011) | 3.33E-08 | 18 | 0.990 | 0.98 |
| rs16852193 *EGFEM1P* | 3 | 168,074,912 | T/C(0.09) | 133,691 | 0.0076 (0.0015) | 8.72E-07 | 41,664 | 0.0005 (0.0030) | 4.34E-01 | 8.86E-02 | 175,355 | 0.0061 (0.0014) | 6.64E-06 | 0 | 0.885 | 0.95 |
| rs228611 *NFKB1* | 4 | 103,561,709 | A/G(0.48) | 133,788 | -0.0055 (0.0009) | 4.66E-10 | 41,657 | -0.0060 (0.0017) | 2.08E-04 | 8.91E-04 | 175,445 | -0.0056 (0.0008) | 3.58E-12 | 4 | 0.998 | 1.00 |
| rs7735249 *ARL15* | 5 | 53,310,139 | C/G(0.92) | 132,513 | -0.0109 (0.0018) | 2.09E-09 | 41,662 | -0.0012 (0.0028) | 3.28E-01 | 6.86E-02 | 174,175 | -0.0079 (0.0015) | 2.08E-07 | 8 | 1.000 | 0.98 |
| rs11960179 *PIK3R1* | 5 | 67,820,217 | A/G(0.12) | 133,714 | -0.0072 (0.0014) | 2.47E-07 | 23,693 | -0.0051 (0.0033) | 6.16E-02 | 2.31E-02 | 157,407 | -0.0069 (0.0013) | 1.57E-07 | 9 | 0.908 | 0.94 |
| rs836788 *DHFR* | 5 | 79,912,044 | T/C(0.35) | 133,810 | -0.0045 (0.0009) | 8.56E-07 | 41,731 | -0.0038 (0.0018) | 1.73E-02 | 9.89E-03 | 175,541 | -0.0043 (0.0008) | 9.89E-08 | 11 | 0.868 | 1.00 |
| rs7759001 *ZNF204* | 6 | 27,341,409 | A/G(0.76) | 133,723 | -0.0053 (0.0010) | 2.64E-07 | 41,760 | -0.0045 (0.0020) | 1.38E-02 | 9.10E-03 | 175,483 | -0.0051 (0.0009) | 1.75E-08 | 0 | 0.930 | 1.00 |
| rs10277115 *UNCX* | 7 | 1,285,195 | A/T(0.24) | 115,895 | 0.0095 (0.0014) | 1.05E-10 | 40,626 | 0.0079 (0.0023) | 3.16E-04 | 9.03E-04 | 156,521 | 0.0090 (0.0012) | 8.72E-14 | 0 | 1.000 | 0.53 |
| rs2290263 *MIR148A* | 7 | 25,887,278 | A/G(0.73) | 132,930 | 0.0053 (0.0010) | 2.35E-07 | 41,756 | 0.0016 (0.0019) | 2.04E-01 | 5.15E-02 | 174,686 | 0.0045 (0.0009) | 6.70E-07 | 5 | 0.959 | 1.00 |
| rs3750082 *KBTBD2* | 7 | 32,919,927 | A/T(0.34) | 127,284 | 0.0049 (0.0009) | 2.52E-07 | 41,210 | 0.0031 (0.0018) | 4.58E-02 | 1.96E-02 | 168,494 | 0.0045 (0.0008) | 3.22E-08 | 2 | 0.934 | 1.00 |
| rs1004402 *GRB10* | 7 | 50,755,208 | A/C(0.12) | 127,292 | 0.0068 (0.0013) | 4.79E-07 | 41,801 | -0.0026 (0.0027) | 8.31E-01 | 1.52E-01 | 169,093 | 0.0050 (0.0012) | 2.93E-05 | 11 | 0.882 | 1.00 |
| rs868055 *UBE2H* | 7 | 129,435,191 | T/C(0.10) | 133,608 | 0.0082 (0.0016) | 3.48E-07 | 41,843 | -0.0008 (0.0029) | 6.14E-01 | 1.22E-01 | 175,451 | 0.0060 (0.0014) | 2.17E-05 | 22 | 0.981 | 0.83 |
| rs6459680 *RNF32* | 7 | 156,258,568 | T/G(0.74) | 133,692 | -0.0065 (0.0010) | 1.96E-10 | 41,655 | -0.0019 (0.0019) | 1.67E-01 | 4.62E-02 | 175,347 | -0.0055 (0.0009) | 1.07E-09 | 0 | 1.000 | 0.98 |
| rs913423 *CYP26A1* | 10 | 94,845,036 | A/G(0.54) | 132,861 | -0.0052 (0.0009) | 5.10E-09 | 41,638 | -0.0014 (0.0017) | 2.07E-01 | 5.15E-02 | 174,499 | -0.0043 (0.0008) | 7.65E-08 | 10 | 0.993 | 1.00 |
| rs4014195 *AP5B1* | 11 | 65,506,822 | C/G(0.64) | 133,723 | 0.0061 (0.0009) | 2.19E-11 | 41,677 | 0.0034 (0.0018) | 2.65E-02 | 1.42E-02 | 175,400 | 0.0055 (0.0008) | 1.10E-11 | 0 | 1.000 | 1.00 |
| rs10491967 *TSPAN9* | 12 | 3,368,093 | A/G(0.11) | 133,800 | -0.0092 (0.0014) | 3.03E-10 | 41,870 | -0.0106 (0.0027) | 4.59E-05 | 3.93E-04 | 175,670 | -0.0095 (0.0013) | 5.18E-14 | 0 | 1.000 | 0.99 |
| rs7956634 *PTPRO* | 12 | 15,321,194 | T/C(0.81) | 133,722 | -0.0068 (0.0011) | 2.46E-09 | 41,726 | -0.0069 (0.0022) | 7.04E-04 | 1.51E-03 | 175,448 | -0.0068 (0.0010) | 7.17E-12 | 0 | 0.997 | 1.00 |

**Supplementary Table 3** (continued).

| SNPID Locus name* | Chr | Position (bp) (Build 37) | Eff./ Non Eff All (EAF)# | STAGE 1 (discovery)† | | | STAGE 2 (replication)‡ | | | | Combined analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Beta (SE) | P-value | N | Beta (SE) | 1-sided P-value | q-value | N | Beta (SE) | P-value | $I^2$ (%) | Power | Median Rsq |
| **eGFRcrea in the overall sample** | | | | | | | | | | | | | | | | |
| rs1106766 *INHBC* | 12 | 57,809,456 | T/C(0.22) | 133,660 | 0.0062 (0.0011) | 4.67E-08 | 21,005 | 0.0058 (0.0026) | 1.23E-02 | 8.79E-03 | 154,665 | 0.0061 (0.0010) | 2.41E-09 | 11 | 0.973 | 0.84 |
| rs11180732 *PHLDA1* | 12 | 76,283,354 | T/G(0.31) | 133,656 | 0.0049 (0.0009) | 4.65E-07 | 41,586 | 0.0008 (0.0018) | 3.26E-01 | 6.86E-02 | 175,242 | 0.0041 (0.0008) | 6.23E-07 | 0 | 0.930 | 0.95 |
| rs2071047 *BMP4* | 14 | 54,418,411 | A/G(0.41) | 133,647 | 0.0044 (0.0009) | 9.15E-07 | 41,772 | 0.0016 (0.0017) | 1.85E-01 | 4.95E-02 | 175,419 | 0.0038 (0.0008) | 3.20E-06 | 13 | 0.879 | 1.00 |
| rs8056893 *SLC7A6* | 16 | 68,304,392 | A/C(0.72) | 133,711 | 0.0051 (0.0010) | 2.03E-07 | 41,695 | 0.0035 (0.0019) | 3.21E-02 | 1.53E-02 | 175,406 | 0.0047 (0.0009) | 1.28E-07 | 0 | 0.940 | 0.98 |
| rs9807656 *SETBP1* | 18 | 42,346,956 | T/C(0.91) | 133,688 | -0.0081 (0.0016) | 6.06E-07 | 40,684 | 0.0020 (0.0029) | 7.61E-01 | 1.42E-01 | 174,372 | -0.0056 (0.0014) | 7.26E-05 | 22 | 0.947 | 0.99 |
| rs9945268 *RNF152* | 18 | 59,340,526 | A/T(0.70) | 127,290 | -0.0048 (0.0010) | 7.05E-07 | 41,612 | -0.0020 (0.0018) | 1.32E-01 | 4.05E-02 | 168,902 | -0.0042 (0.0009) | 3.18E-06 | 0 | 0.876 | 1.00 |
| rs11666497 *SIPA1L3* | 19 | 38,464,262 | T/C(0.18) | 127,271 | -0.0064 (0.0012) | 8.58E-08 | 41,640 | -0.0041 (0.0022) | 3.06E-02 | 1.53E-02 | 168,911 | -0.0058 (0.0011) | 4.25E-08 | 24 | 0.973 | 0.97 |
| rs12975033 *IZUMO1* | 19 | 49,249,443 | A/T(0.55) | 133,724 | -0.0052 (0.0009) | 4.75E-09 | 38,469 | 0.0006 (0.0017) | 6.43E-01 | 1.22E-01 | 172,193 | -0.0039 (0.0008) | 1.31E-06 | 26 | 0.992 | 1.00 |
| rs6088580 *TP53INP2* | 20 | 33,285,053 | C/G(0.47) | 132,773 | -0.0055 (0.0009) | 7.17E-10 | 34,592 | -0.0027 (0.0017) | 6.28E-02 | 2.31E-02 | 167,365 | -0.0049 (0.0008) | 1.79E-09 | 0 | 0.997 | 0.99 |
| rs2235808 *JPH2* | 20 | 42,815,795 | C/G(0.85) | 129,605 | 0.0071 (0.0013) | 1.50E-07 | 25,036 | 0.0020 (0.0025) | 2.17E-01 | 5.17E-02 | 154,641 | 0.0060 (0.0012) | 3.21E-07 | 0 | 0.967 | 0.87 |
| rs17216707 *BCAS1* | 20 | 52,732,362 | T/C(0.79) | 133,656 | -0.0084 (0.0011) | 5.96E-13 | 39,971 | -0.0051 (0.0021) | 7.80E-03 | 6.69E-03 | 173,627 | -0.0077 (0.0010) | 8.83E-15 | 1 | 1.000 | 0.85 |
| **CKD in the overall sample** | | | | | | | | | | | | | | | | |
| rs1032843 *FIGN* | 2 | 164,184,329 | T/C(0.07) | 118,131 | 0.1508 (0.0299) | 4.48E-07 | 32,338 | 0.0332 (0.0486) | 2.47E-01 | 5.72E-02 | 150,469 | 0.1174 (0.0259) | 5.70E-06 | 2 | 0.915 | 0.95 |
| rs11039182 *MADD* | 11 | 47,346,723 | T/C(0.70) | 118,130 | -0.0818 (0.0167) | 9.07E-07 | 35,062 | -0.0325 (0.0271) | 1.15E-01 | 3.66E-02 | 153,192 | -0.0678 (0.0144) | 2.64E-06 | 0 | 0.722 | 0.99 |
| rs593790 *OR4C45* | 11 | 48,391,116 | A/T(0.82) | 118,137 | -0.1045 (0.0209) | 5.96E-07 | 35,015 | -0.0213 (0.0320) | 2.53E-01 | 5.72E-02 | 153,152 | -0.0788 (0.0178) | 9.77E-06 | 0 | 0.956 | 0.99 |
| rs2832559 *GRIK1* | 21 | 31,417,144 | T/C(0.91) | 117,017 | -0.1435 (0.0292) | 9.56E-07 | 30,577 | 0.0668 (0.0540) | 8.92E-01 | 1.61E-01 | 147,594 | -0.0941 (0.0262) | 3.31E-04 | 0 | 0.889 | 0.97 |

**Supplementary Table 3** (continued).

| SNPID Locus name* | Chr | Position (bp) (Build 37) | Eff./ Non Eff All (EAF)# | STAGE 1 (discovery)† | | | STAGE 2 (replication)‡ | | | | Combined analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Beta (SE) | P-value | N | Beta (SE) | 1-sided P-value | q-value | N | Beta (SE) | P-value | $I^2$ (%) | Power | Median Rsq |
| **eGFRcys in the overall sample** | | | | | | | | | | | | | | | | |
| rs12428035 *DZIP1* | 13 | 96,300,872 | T/C(0.12) | 33,145 | -0.0144 (0.0029) | 7.28E-07 | 14,919 | -0.0089 (0.0039) | 1.13E-02 | 8.79E-03 | 48,064 | -0.0125 (0.0023) | 6.33E-08 | 0 | 0.588 | 1.00 |

*Based on Table 1 for replicated loci and on the closest gene name for the non-replicated loci, according to the UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly.
#Effect Allele Frequency as estimated in the combined sample.
†All P-values and SEs reported from the STAGE 1 analysis were twice-GC corrected, to account for possible genomic inflation.
‡ In Stage 2 analysis, 1-sided P-values were computed to assess direction consistent effects with Stage 1; q-values were estimated based on the 1-sided P-values.

**Supplementary Table 4**. Association of replicated novel loci with eGFRcrea, CKD, and eGFRcys, in the overall combined sample.

| | | | | | eGFRcrea | | | CKD | | eGFRcys | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNP ID** | **Chr** | **Position (bp) (Build 37)** | **Locus name*** | **Eff./ Non Eff. All. (EAF)** | **beta (SE)** | **P-value** | **beta (SE) from random-effect meta-analysis** | **OR (95%CI)** | **P-value** | **beta (SE)** | **P-value** |
| rs12136063 | 1 | 110,014,170 | *SYPL2* | A/G(0.70) | 0.0045(0.0008) | 4.71E-08 | 0.0045(0.0008) | 0.98(0.96,1.01) | 2.37E-01 | 0.0025(0.0016) | 1.25E-01 |
| rs3850625 | 1 | 201,016,296 | *CACNA1S* | A/G(0.12) | 0.0078(0.0013) | 5.53E-10 | 0.0079(0.0012) | 0.95(0.91,0.99) | 2.31E-02 | 0.0016(0.0023) | 4.95E-01 |
| rs2802729 | 1 | 243,501,763 | *SDCCAG8* | A/C(0.43) | -0.0046(0.0008) | 2.20E-08 | -0.0047(0.0009) | 1.05(1.02,1.08) | 4.10E-04 | -0.0036(0.0016) | 2.49E-02 |
| rs4667594 | 2 | 170,008,506 | *LRP2* | A/T(0.53) | -0.0044(0.0008) | 3.52E-08 | -0.0045(0.0008) | 1.05(1.02,1.07) | 5.43E-04 | 0.0001(0.0015) | 9.63E-01 |
| rs2712184 | 2 | 217,682,779 | *IGFBP5* | A/C(0.58) | -0.0048(0.0008) | 3.02E-09 | -0.0047(0.0009) | 1.02(0.99,1.05) | 1.54E-01 | 0.0001(0.0015) | 9.39E-01 |
| rs6795744 | 3 | 13,906,850 | *WNT7A* | A/G(0.15) | 0.0060(0.0011) | 3.33E-08 | 0.0057(0.0013) | 0.96(0.93,1.00) | 3.98E-02 | 0.0049(0.0021) | 1.84E-02 |
| rs9682041 | 3 | 170,091,902 | *SKIL* | T/C(0.87) | -0.0062(0.0012) | 2.95E-07 | -0.0062(0.0012) | 1.02(0.98,1.06) | 2.53E-01 | -0.0039(0.0022) | 7.99E-02 |
| rs10513801 | 3 | 185,822,353 | *ETV5* | T/G(0.87) | 0.0070(0.0012) | 2.47E-09 | 0.0069(0.0012) | 0.93(0.89,0.96) | 5.08E-05 | 0.0019(0.0023) | 3.92E-01 |
| rs228611 | 4 | 103,561,709 | *NFKB1* | A/G(0.47) | -0.0056(0.0008) | 3.58E-12 | -0.0056(0.0008) | 1.03(1.00,1.05) | 3.36E-02 | -0.0023(0.0015) | 1.23E-01 |
| rs7759001 | 6 | 27,341,409 | *ZNF204* | A/G(0.76) | -0.0051(0.0009) | 1.75E-08 | -0.0052(0.0009) | 1.03(1.00,1.06) | 5.66E-02 | -0.0023(0.0017) | 1.71E-01 |
| rs10277115 | 7 | 1,285,195 | *UNCX* | A/T(0.23) | 0.0090(0.0012) | 8.72E-14 | 0.0090(0.0012) | 0.96(0.92,1.00) | 4.09E-02 | 0.0045(0.0025) | 7.62E-02 |
| rs3750082 | 7 | 32,919,927 | *KBTBD2* | A/T(0.33) | 0.0045(0.0008) | 3.22E-08 | 0.0045(0.0009) | 0.97(0.95,1.00) | 5.76E-02 | 0.0014(0.0016) | 3.95E-01 |
| rs6459680 | 7 | 156,258,568 | *RNF32* | T/G(0.74) | -0.0055(0.0009) | 1.07E-09 | -0.0055(0.0009) | 1.04(1.01,1.07) | 2.08E-02 | -0.0043(0.0017) | 1.06E-02 |
| rs10994860 | 10 | 52,645,424 | *A1CF* | T/C(0.19) | 0.0071(0.0010) | 1.66E-12 | 0.0069(0.0011) | 0.99(0.95,1.02) | 5.14E-01 | 0.0015(0.0020) | 4.41E-01 |
| rs163160 | 11 | 2,789,955 | *KCNQ1* | A/G(0.82) | 0.0064(0.0010) | 1.72E-10 | 0.0063(0.0011) | 0.95(0.92,0.99) | 5.30E-03 | 0.0073(0.0020) | 2.35E-04 |
| rs4014195 | 11 | 65,506,822 | *AP5B1* | C/G(0.64) | 0.0055(0.0008) | 1.10E-11 | 0.0056(0.0004) | 0.93(0.91,0.96) | 2.35E-07 | 0.0053(0.0015) | 5.58E-04 |
| rs10491967 | 12 | 3,368,093 | *TSPAN9* | A/G(0.10) | -0.0095(0.0013) | 5.18E-14 | -0.0095(0.0013) | 1.06(1.02,1.11) | 6.54E-03 | -0.0024(0.0024) | 3.24E-01 |
| rs7956634 | 12 | 15,321,194 | *PTPRO* | T/C(0.81) | -0.0068(0.0010) | 7.17E-12 | -0.0066(0.0011) | 1.03(1.00,1.06) | 8.94E-02 | -0.0059(0.0019) | 2.17E-03 |
| rs1106766 | 12 | 57,809,456 | *INHBC* | T/C(0.22) | 0.0061(0.0010) | 2.41E-09 | 0.0060(0.0011) | 0.98(0.95,1.02) | 3.07E-01 | 0.0048(0.0019) | 1.03E-02 |
| rs164748 | 16 | 89,708,292 | *DPEP1* | C/G(0.53) | 0.0042(0.0008) | 1.63E-07 | 0.0040(0.0010) | 0.99(0.96,1.01) | 3.27E-01 | 0.0046(0.0015) | 1.80E-03 |
| rs8091180 | 18 | 77,164,243 | *NFATC1* | A/G(0.56) | -0.0053(0.0009) | 5.57E-09 | -0.0053(0.0009) | 1.03(1.00,1.06) | 3.57E-02 | -0.0050(0.0020) | 1.19E-02 |
| rs11666497 | 19 | 38,464,262 | *SIPA1L3* | T/C(0.18) | -0.0058(0.0011) | 4.25E-08 | -0.0061(0.0013) | 1.00(0.97,1.04) | 9.70E-01 | -0.0027(0.0019) | 1.70E-01 |
| rs6088580 | 20 | 33,285,053 | *TP53INP2* | C/G(0.47) | -0.0049(0.0008) | 1.79E-09 | -0.0049(0.0008) | 1.04(1.01,1.07) | 5.25E-03 | 0.0000(0.0015) | 9.92E-01 |
| rs17216707 | 20 | 52,732,362 | *BCAS1* | T/C(0.79) | -0.0077(0.0010) | 8.83E-15 | -0.0076(0.0011) | 1.05(1.01,1.09) | 8.18E-03 | -0.0083(0.0020) | 3.25E-05 |

* Conventional locus name based on relevant genes in the region as identified by bioinformatic investigation (Suppl. Tab. 12) or closest gene. A complete overview of the genes in each locus is given in the regional association plots (Suppl. Fig. 4)

**Supplementary Table 5**. SNP associations for novel and known loci stratified by diabetes status.

| SNP ID (effect allele) | Locus name | No Diabetes | | | Diabetes | | | P-value for difference* |
|---|---|---|---|---|---|---|---|---|
| | | N | beta (SE) | P-value | N | beta (SE) | P-value | |
| **Novel loci**: sample size based on the combined (discovery and replication) sample | | | | | | | | |
| rs3850625 (A) | *CACNA1S* | 153,107 | 0.0083 (0.0013) | 6.82E-11 | 16,275 | 0.0038 (0.0048) | 4.34E-01 | 0.27 |
| rs2712184 (A) | *IGFBP5* | 153,854 | -0.0053 (0.0004) | 1.33E-10 | 16,463 | -0.0034 (0.0031) | 2.70E-01 | 0.22 |
| rs9682041 (T) | *SKIL* | 150,911 | -0.0068 (0.0012) | 2.58E-08 | 16,161 | 0.0006 (0.0045) | 8.86E-01 | 0.20 |
| rs10513801 (T) | *ETV5* | 154,774 | 0.0072 (0.0012) | 1.03E-09 | 16,470 | 0.0022 (0.0045) | 6.19E-01 | 0.28 |
| rs10994860 (T) | *A1CF* | 154,644 | 0.0077 (0.0011) | 1.07E-12 | 16,451 | 0.0031 (0.0041) | 4.57E-01 | 0.27 |
| rs163160 (A) | *KCNQ1* | 154,684 | 0.0065 (0.0011) | 2.26E-09 | 16,457 | 0.0055 (0.0040) | 1.68E-01 | 0.81 |
| rs164748 (C) | *DPEP1* | 154,497 | 0.0046 (0.0004) | 1.95E-08 | 16,416 | 0.0026 (0.0031) | 4.07E-01 | 0.52 |
| rs8091180 (A) | *NFATC1* | 153,715 | -0.0060 (0.0010) | 1.28E-09 | 13,764 | 0.0030 (0.0043) | 4.85E-01 | 0.04 |
| rs12136063 (A) | *SYPL2* | 152,998 | 0.0043 (0.0009) | 2.25E-06 | 16,253 | 0.0013 (0.0034) | 7.02E-01 | 0.38 |
| rs2802729 (A) | *SDCCAG8* | 152,501 | -0.0042 (0.0009) | 2.65E-06 | 16,156 | -0.0050 (0.0033) | 1.24E-01 | 0.81 |
| rs4667594 (A) | *LRP2* | 154,570 | -0.0042 (0.0008) | 2.09E-07 | 16,449 | -0.0034 (0.0031) | 2.67E-01 | 0.80 |
| rs6795744 (A) | *WNT7A* | 154,716 | 0.0053 (0.0011) | 1.23E-06 | 16,462 | 0.0070 (0.0043) | 1.02E-01 | 0.70 |
| rs228611 (A) | *NFKB1* | 154,683 | -0.0056 (0.0008) | 7.39E-12 | 16,454 | -0.0077 (0.0030) | 1.07E-02 | 0.49 |
| rs7759001 (A) | *ZNF204* | 154,713 | -0.0053 (0.0009) | 1.02E-08 | 16,458 | -0.0000 (0.0036) | 9.92E-01 | 0.15 |
| rs10277115 (A) | *UNCX* | 141,932 | 0.0085 (0.0013) | 4.97E-11 | 13,565 | 0.0156 (0.0053) | 3.30E-03 | 0.19 |
| rs3750082 (A) | *KBTBD2* | 148,429 | 0.0042 (0.0009) | 3.82E-06 | 15,754 | 0.0050 (0.0033) | 1.32E-01 | 0.81 |
| rs6459680 (T) | *RNF32* | 154,586 | -0.0057 (0.0009) | 4.64E-10 | 16,454 | -0.0043 (0.0035) | 2.25E-01 | 0.70 |
| rs4014195 (C) | *AP5B1* | 154,634 | 0.0050 (0.0008) | 1.02E-09 | 16,452 | 0.0116 (0.0032) | 2.52E-04 | 0.04 |
| rs10491967 (A) | *TSPAN9* | 154,881 | -0.0089 (0.0013) | 3.18E-11 | 16,477 | -0.0204 (0.0050) | 3.80E-05 | 0.02 |
| rs7956634 (T) | *PTPRO* | 154,677 | -0.0065 (0.0010) | 1.11E-10 | 16,460 | -0.0076 (0.0038) | 4.82E-02 | 0.78 |
| rs1106766 (T) | *INHBC* | 138,058 | 0.0063 (0.0010) | 1.75E-09 | 14,990 | 0.0016 (0.0040) | 6.89E-01 | 0.25 |
| rs11666497 (T) | *SIPA1L3* | 148,770 | -0.0058 (0.0011) | 6.04E-08 | 15,831 | -0.0096 (0.0041) | 2.01E-02 | 0.37 |
| rs6088580 (C) | *TP53INP2* | 150,326 | -0.0050 (0.0008) | 1.51E-09 | 15,387 | -0.0010 (0.0031) | 7.48E-01 | 0.21 |
| rs17216707 (T) | *BCAS1* | 153,362 | -0.0075 (0.0011) | 2.25E-12 | 15,977 | -0.0063 (0.0039) | 1.06E-01 | 0.76 |
| **Known loci:** sample size based on the discovery sample | | | | | | | | |
| rs12917707 (T) | *UMOD* | 118,365 | 0.0152 (0.0012) | 4.68E-36 | 11,522 | 0.0266 (0.0048) | 2.48E-08 | 0.02 |
| rs1260326 (T) | *GCKR* | 118,415 | 0.0065 (0.0009) | 1.86E-12 | 11,525 | 0.0112 (0.0037) | 2.21E-03 | 0.21 |
| rs6465825 (T) | *SLC22A2* | 118,448 | 0.0061 (0.0009) | 4.80E-11 | 11,529 | 0.0089 (0.0036) | 1.44E-02 | 0.45 |
| rs2279463 (A) | *VEGFA* | 118,368 | 0.0119 (0.0014) | 6.98E-18 | 11,521 | 0.0062 (0.0053) | 2.43E-01 | 0.30 |
| rs12124078 (A) | *CASP9* | 116,718 | 0.0058 (0.0010) | 4.54E-09 | 11,315 | 0.0039 (0.0039) | 3.18E-01 | 0.63 |
| rs848490 (C) | *TMEM60* | 112,566 | 0.0074 (0.0010) | 1.35E-12 | 10,897 | 0.0033 (0.0041) | 4.30E-01 | 0.33 |
| rs2928148 (A) | *INO80* | 118,368 | 0.0050 (0.0009) | 2.82E-08 | 11,521 | 0.0026 (0.0035) | 4.73E-01 | 0.50 |
| rs9895661 (T) | *BCAS3* | 118,188 | 0.0121 (0.0012) | 2.80E-22 | 11,520 | -0.0006 (0.0048) | 9.00E-01 | 0.01 |
| rs347685 (A) | *TFDP2* | 118,374 | -0.0077 (0.0010) | 1.70E-14 | 11,522 | -0.0021 (0.0040) | 5.93E-01 | 0.17 |
| rs7208487 (T) | *CDK12* | 118,453 | -0.0091 (0.0012) | 8.60E-14 | 11,526 | -0.0024 (0.0048) | 6.20E-01 | 0.17 |

**Supplementary Table 5** (continued).

| SNP ID (effect allele) | Locus name | No Diabetes | | | Diabetes | | | P-value for difference* |
|---|---|---|---|---|---|---|---|---|
| | | N | beta (SE) | P-value | N | beta (SE) | P-value | |
| **Known loci:** sample size based on the discovery sample | | | | | | | | |
| rs10774021 (T) | *SLC6A13* | 118,448 | -0.0067 (0.0009) | 1.48E-12 | 11,526 | -0.0031 (0.0038) | 4.13E-01 | 0.35 |
| rs2453580 (T) | *SLC47A1* | 117,386 | 0.0073 (0.0010) | 2.56E-13 | 11,474 | -0.0035 (0.0040) | 3.93E-01 | 0.01 |
| rs4744712 (A) | *PIP5K1B* | 118,374 | -0.0072 (0.0009) | 7.45E-15 | 11,518 | -0.0053 (0.0037) | 1.48E-01 | 0.62 |
| rs12460876 (T) | *SLC7A9* | 118,361 | -0.0065 (0.0009) | 2.86E-12 | 11,521 | -0.0062 (0.0037) | 9.16E-02 | 0.94 |
| rs881858 (A) | *SLC34A1* | 118,324 | -0.0081 (0.0011) | 4.03E-14 | 11,521 | -0.0063 (0.0042) | 1.35E-01 | 0.68 |
| rs10109414 (T) | *STC1* | 118,342 | -0.0075 (0.0009) | 3.53E-16 | 11,521 | -0.0066 (0.0036) | 6.75E-02 | 0.81 |
| rs6431731 (T) | *DDX1* | 109,308 | -0.0124 (0.0025) | 4.70E-07 | 10,419 | -0.0070 (0.0100) | 4.89E-01 | 0.60 |
| rs626277 (A) | *DACH1* | 118,450 | -0.0049 (0.0009) | 1.44E-07 | 11,528 | -0.0072 (0.0036) | 4.53E-02 | 0.53 |
| rs17319721 (A) | *SHROOM3* | 118,359 | -0.0113 (0.0009) | 5.08E-35 | 11,522 | -0.0075 (0.0036) | 3.64E-02 | 0.30 |
| rs13538 (A) | *ALMS1* | 115,154 | -0.0092 (0.0011) | 2.79E-16 | 11,135 | -0.0077 (0.0045) | 8.45E-02 | 0.74 |
| rs11959928 (A) | *DAB2* | 118,359 | -0.0082 (0.0009) | 7.14E-19 | 11,521 | -0.0078 (0.0036) | 3.33E-02 | 0.91 |
| rs2453533 (A) | *GATM* | 118,374 | -0.0125 (0.0009) | 4.83E-41 | 11,520 | -0.0079 (0.0036) | 3.16E-02 | 0.21 |
| rs7805747 (A) | *PRKAG2* | 116,602 | -0.0136 (0.0012) | 1.53E-29 | 11,378 | -0.0085 (0.0048) | 7.37E-02 | 0.30 |
| rs1394125 (A) | *UBE2Q2* | 118,404 | -0.0072 (0.0010) | 5.83E-13 | 11,525 | -0.0089 (0.0041) | 2.92E-02 | 0.69 |
| rs3925584 (T) | *MPPED2* | 118,345 | -0.0074 (0.0009) | 5.35E-16 | 11,521 | -0.0100 (0.0035) | 5.00E-03 | 0.47 |
| rs267734 (T) | *LASS2* | 116,718 | -0.0079 (0.0011) | 2.81E-12 | 11,315 | -0.0110 (0.0045) | 1.39E-02 | 0.50 |
| rs7422339 (A) | *CPS1* | 115,499 | -0.0106 (0.0011) | 3.25E-22 | 11,422 | -0.0137 (0.0043) | 1.61E-03 | 0.48 |
| rs10794720 (T) | *WDR37* | 118,433 | -0.0093 (0.0017) | 4.95E-08 | 11,528 | -0.0145 (0.0067) | 3.06E-02 | 0.45 |
| rs491567 (A) | *WDR72* | 118,374 | -0.0078 (0.0011) | 1.45E-12 | 11,521 | -0.0167 (0.0043) | 1.25E-04 | 0.04 |

* P-value of a two-sample *t* test for correlated data (see Methods: “Associations Stratified by Diabetes and Hypertension Status“).

**Supplementary Table 6**. Association between replicated SNPs and additional kidney related phenotypes.*

| | | | Myocardial Infarction | | Left Ventricular Mass | | Incident Heart Failure | | DBP | | SBP | | UACR | | Fasting glucose | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNPID** | **Locus name** | **All.#** | **OR (95%CI)** | **P-value** | **beta (SE)** | **P-value** | **beta (SE)** | **P-value** | **beta (SE)** | **P-value** | **beta (SE)** | **P-value** | **beta(SE)** | **P-value** | **beta (SE)** | **P-value** |
| rs3850625 | *CACNA1S* | A/G | 1.03 (0.99,1.08) | 0.15 | 0.390 (0.680) | 0.57 | -0.034 (0.044) | 0.44 | 0.003 (0.094) | 0.97 | -0.068 (0.147) | 0.64 | 0.017 (0.011) | 0.11 | 0.012 (0.005) | 0.013 |
| rs2712184 | *IGFBP5* | A/C | 1.00 (0.97,1.03) | 0.81 | -0.183 (0.449) | 0.68 | -0.051 (0.034) | 0.14 | -0.087 (0.062) | 0.16 | -0.016 (0.098) | 0.87 | -0.001 (0.006) | 0.88 | -0.001 (0.003) | 0.77 |
| rs9682041 | *SKIL* | T/C | 0.99 (0.95,1.04) | 0.79 | -0.036 (0.639) | 0.96 | -0.003 (0.043) | 0.95 | -0.026 (0.093) | 0.78 | -0.092 (0.147) | 0.53 | -0.015 (0.009) | 0.11 | -0.006 (0.005) | 0.18 |
| rs10513801 | *ETV5* | T/G | 0.97 (0.94,1.01) | 0.18 | 0.255 (0.649) | 0.69 | 0.019 (0.044) | 0.67 | -0.021 (0.091) | 0.82 | 0.004 (0.145) | 0.98 | 0.027 (0.011) | 0.014 | 0.002 (0.005) | 0.71 |
| rs10994860 | *A1CF* | T/C | 0.99 (0.96,1.03) | 0.56 | 0.294 (0.595) | 0.62 | -0.081 (0.041) | 0.05 | -0.064 (0.081) | 0.43 | -0.162 (0.127) | 0.20 | -0.006 (0.009) | 0.55 | 0.004 (0.004) | 0.28 |
| rs163160 | *KCNQ1* | A/G | 0.98 (0.95,1.02) | 0.39 | 0.360 (0.577) | 0.53 | -0.063 (0.038) | 0.10 | -0.040 (0.082) | 0.62 | 0.032 (0.129) | 0.80 | 0.011 (0.010) | 0.26 | 0.001 (0.004) | 0.86 |
| rs164748 | *DPEP1* | C/G | 0.99 (0.97,1.02) | 0.65 | 0.668 (0.439) | 0.13 | 0.062 (0.029) | 0.04 | 0.173 (0.063) | 0.01 | 0.361 (0.099) | 0.00026§ | 0.021 (0.006) | 0.0004 | -0.003 (0.003) | 0.30 |
| rs8091180 | *NFATC1* | A/G | NA | NA | 0.307 (0.816) | 0.71 | 0.056 (0.044) | 0.21 | 0.122 (0.103) | 0.23 | 0.181 (0.162) | 0.27 | -0.018 (0.015) | 0.21 | 0.006 (0.005) | 0.19 |
| rs12136063 | *SYPL2* | A/G | 1.03 (1.00,1.06) | 0.08 | -0.192 (0.478) | 0.69 | 0.023 (0.032) | 0.47 | 0.032 (0.066) | 0.62 | -0.033 (0.104) | 0.75 | 0.010 (0.008) | 0.19 | -0.007 (0.003) | 0.05 |
| rs2802729 | *SDCCAG8* | A/C | NA | NA | -0.127 (0.470) | 0.79 | -0.005 (0.032) | 0.88 | 0.147 (0.067) | 0.03 | 0.239 (0.105) | 0.02 | 0.008 (0.007) | 0.23 | 0.002 (0.003) | 0.53 |
| rs4667594 | *LRP2* | A/T | 0.99 (0.97,1.02) | 0.59 | 0.940 (0.440) | 0.03 | 0.019 (0.029) | 0.51 | 0.098 (0.062) | 0.11 | 0.152 (0.097) | 0.12 | -0.008 (0.006) | 0.18 | 0.000 (0.003) | 0.89 |
| rs6795744 | *WNT7A* | A/G | 0.98 (0.94,1.02) | 0.27 | 0.298 (0.643) | 0.64 | -0.071 (0.045) | 0.12 | -0.022 (0.088) | 0.80 | -0.110 (0.139) | 0.43 | -0.005 (0.009) | 0.57 | 0.005 (0.004) | 0.30 |
| rs228611 | *NFKB1* | A/G | 0.98 (0.95,1.01) | 0.18 | 0.165 (0.440) | 0.71 | 0.008 (0.028) | 0.78 | 0.090 (0.061) | 0.14 | 0.003 (0.097) | 0.98 | 0.008 (0.006) | 0.20 | 0.011 (0.003) | 0.00026§ |
| rs7759001 | *ZNF204* | A/G | 0.99 (0.96,1.02) | 0.51 | 0.172 (0.524) | 0.74 | -0.031 (0.034) | 0.36 | -0.022 (0.071) | 0.75 | -0.085 (0.112) | 0.45 | 0.002 (0.007) | 0.83 | 0.006 (0.004) | 0.10 |
| rs10277115 | *UNCX* | A/T | NA | NA | -1.058 (0.777) | 0.17 | 0.012 (0.052) | 0.82 | -0.099 (0.141) | 0.48 | -0.232 (0.219) | 0.29 | 0.013 (0.012) | 0.27 | -0.009 (0.006) | 0.15 |
| rs3750082 | *KBTBD2* | A/T | 0.99 (0.96,1.02) | 0.48 | 0.641 (0.470) | 0.17 | -0.005 (0.031) | 0.86 | -0.024 (0.066) | 0.72 | 0.094 (0.104) | 0.37 | 0.019 (0.006) | 0.0036 | -0.001 (0.003) | 0.88 |
| rs6459680 | *RNF32* | T/G | 0.98 (0.95,1.01) | 0.14 | -0.234 (0.514) | 0.65 | -0.010 (0.034) | 0.76 | -0.155 (0.071) | 0.03 | -0.184 (0.112) | 0.10 | -0.001 (0.008) | 0.90 | 0.002 (0.004) | 0.60 |
| rs4014195 | *AP5B1* | C/G | 0.98 (0.95,1.01) | 0.20 | -0.825 (0.458) | 0.07 | -0.052 (0.035) | 0.14 | -0.079 (0.064) | 0.22 | -0.176 (0.101) | 0.08 | 0.007 (0.006) | 0.29 | 0.001 (0.003) | 0.70 |

**Supplementary Table 6** (continued).

| | | | Myocardial Infarction | | Left Ventricular Mass | | Incident Heart Failure | | DBP | | SBP | | UACR | | Fasting glucose | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNPID** | **Locus name** | **All.** # | **OR (95%CI)** | **P-value** | **beta (SE)** | **P-value** | **beta (SE)** | **P-value** | **beta (SE)** | **P-value** | **beta (SE)** | **P-value** | **beta(SE)** | **P-value** | **beta (SE)** | **P-value** |
| rs10491967 | *TSPAN9* | A/G | 0.95 (0.91,1.00) | 0.04 | 0.087 (0.696) | 0.90 | -0.033 (0.047) | 0.48 | 0.003 (0.101) | 0.98 | -0.205 (0.160) | 0.20 | 0.002 (0.011) | 0.86 | -0.003 (0.005) | 0.60 |
| rs7956634 | *PTPRO* | T/C | 1.01 (0.98,1.05) | 0.49 | 0.528 (0.564) | 0.35 | 0.010 (0.036) | 0.79 | 0.047 (0.083) | 0.57 | 0.113 (0.130) | 0.39 | -0.017 (0.008) | 0.03 | 0.006 (0.004) | 0.17 |
| rs1106766 | *INHBC* | T/C | 0.99 (0.96,1.02) | 0.56 | -0.322 (0.584) | 0.58 | 0.027 (0.037) | 0.46 | 0.069 (0.079) | 0.39 | 0.093 (0.125) | 0.46 | 0.011 (0.009) | 0.22 | -0.001 (0.004) | 0.82 |
| rs11666497 | *SIPA1L3* | T/C | 1.02 (0.98,1.05) | 0.42 | 0.624 (0.590) | 0.29 | 0.058 (0.041) | 0.15 | -0.056 (0.081) | 0.49 | -0.034 (0.127) | 0.79 | 0.000 (0.008) | 1.00 | 0.002 (0.004) | 0.72 |
| rs6088580 | *TP53INP2* | C/G | 1.02 (0.99,1.05) | 0.14 | -0.864 (0.456) | 0.06 | 0.014 (0.028) | 0.63 | -0.126 (0.061) | 0.04 | -0.066 (0.097) | 0.49 | 0.010 (0.006) | 0.10 | 0.010 (0.003) | 0.0016 |
| rs17216707 | *BCAS1* | T/C | 1.02 (0.98,1.05) | 0.40 | 0.238 (0.605) | 0.69 | 0.038 (0.041) | 0.35 | 0.136 (0.084) | 0.11 | 0.195 (0.132) | 0.14 | -0.000 (0.009) | 0.98 | 0.004 (0.004) | 0.36 |

* ***Myocardial infarction***: results from CARDIoGRAM meta-analysis[8] of up to 14 studies, for a total sample size comprised between 72,649 and 83,231, except for SNPs rs4014195 (N=61,259) and rs2712184 (N=61,275). SNPs not reported did not pass CARDIoGRAM internal quality control checks and were not assessed. ***Left Ventricular Mass*****:** per-allele effect on left ventricular mass in grams, from a meta-analysis of five community-based studies within the EchoGen consortium, totaling 12,612 European ancestry individuals.[9] ***Incident heart failure***: CHARGE consortium meta-analysis on incident heart failure:[10] four studies on European ancestry individuals totaling a sample size of 20,926, except for SNPs rs2712184 and rs4014195 (N=13,282). ***DBP*** and ***SBP***: diastolic and systolic blood pressure results from the ICBP consortium:[11] meta-analysis of up to 43 studies, for a total sample size of 53,302 to 69,671 samples, except for SNPs rs10277115 (27 studies; N=17,644) and rs8091180 (21 studies; N=23,456). ***UACR***: urinary albumin-to-creatinine ratio, results from the CKDGen consortium (personal communication): meta-analysis of up to 29 studies, for a total sample size of 39,130 to 54,450. ***Fasting glucose***: per-allele effect on fasting glucose (mmol/L) not adjusted for BMI in 29 studies on up 58,074 non-diabetic participants of European ancestry.[12]

# All.: first is the effect and second is the non-effect allele, respectively.

§ P-values that are significant at a Bonferroni corrected level of 0.0003, corresponding to 0.05 over 165 tests.

**Supplementary Table 7**. NHGRI GWAS catalog query of novel loci associated with different traits at a genome-wide significant level.

| Locus name | Index SNP | Published SNP | Chr | Position (Build 37) | Region | LD ($r^2$)* | Disease or Quantitative Trait[REF] | P-value |
|---|---|---|---|---|---|---|---|---|
| *SDCCAG8* | rs2802729 | rs6703335 | 1 | 243,608,967 | 1q43 | 0.44 | Schizophrenia[13] | 5.00E-08 |
| *ETV5* | rs10513801 | rs1516725 | 3 | 185,824,004 | 3q27.2 | 1.00 | Body mass index[14] | 4.00E-08 |
| | | rs1516725 | 3 | 185,824,004 | 3q27.2 | 1.00 | Obesity[14] | 3.00E-09 |
| | | rs7647305 | 3 | 185,834,290 | 3q27.2 | 0.39 | Body mass index[15] | 7.00E-11 |
| | | rs7647305 | 3 | 185,834,290 | 3q27.2 | 0.39 | Weight[15] | 4.00E-09 |
| | | rs9816226 | 3 | 185,834,499 | 3q27.2 | 0.49 | Obesity[14] | 2.00E-13 |
| | | rs9816226 | 3 | 185,834,499 | 3q27.2 | 0.49 | Obesity[14] | 2.00E-14 |
| | | rs9816226 | 3 | 185,834,499 | 3q27.2 | 0.49 | Body mass index[16] | 2.00E-18 |
| *NFKB1* | rs228611 | rs3774959 | 4 | 103,511,114 | 4q24 | 0.29 | Ulcerative colitis[17] | 4.00E-12 |
| | | rs7665090 | 4 | 103,551,603 | 4q24 | 0.87 | Primary biliary cirrhosis[18] | 4.00E-12 |
| *UNCX* | rs10277115 | rs10275044 | 7 | 1,273,845 | 7p22.3 | 0.73 | Blood Urea Nitrogen[19] | 4.00E-09 |
| | | rs10277115 | 7 | 1,285,195 | 7p22.3 | 1.00 | eGRFcrea[19] | 1.00E-10 |
| | | rs10277115 | 7 | 1,285,195 | 7p22.3 | 1.00 | Serum creatinine[19] | 5.00E-11 |
| *A1CF* | rs10994860 | rs10821905 | 10 | 52,646,093 | 10q11.23 | 1.00 | Urate levels[20] | 7.00E-17 |
| *AP5B1* | rs4014195 | rs479844 | 11 | 65,551,957 | 11q13.1 | 0.37 | Atopic dermatitis[21] | 1.00E-13 |
| | | rs642803 | 11 | 65,560,620 | 11q13.1 | 0.40 | Urate levels[20] | 3.00E-13 |
| *INHBC* | rs1106766 | rs11613352 | 12 | 57,792,580 | 12q13.3 | 1.00 | HDL cholesterol[22] | 2.00E-08 |
| | | rs11613352 | 12 | 57,792,580 | 12q13.3 | 1.00 | Triglycerides[22] | 4.00E-10 |
| | | rs1106766 | 12 | 57,809,456 | 12q13.3 | 1.00 | Urate levels[23] | 2.00E-11 |
| | | rs3741414 | 12 | 57,844,049 | 12q13.3 | 0.97 | Urate levels[20] | 2.00E-25 |
| *DPEP1* | rs164748 | rs154657 | 16 | 89,708,096 | 16q24.3 | 1.00 | Homocysteine levels[24] | 2.00E-43 |
| | | rs258322 | 16 | 89,755,903 | 16q24.3 | 0.30 | Melanoma[25] | 3.00E-27 |
| | | rs258322 | 16 | 89,755,903 | 16q24.3 | 0.30 | Melanoma[26] | 3.00E-27 |
| | | rs258322 | 16 | 89,755,903 | 16q24.3 | 0.30 | Black vs. red hair color[27] | 2.00E-23 |
| | | rs12921383 | 16 | 89,859,753 | 16q24.3 | 0.25 | Homocysteine levels[24] | 8.00E-11 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Hair color[28] | 3.00E-09 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Non-melanoma skin cancer[28] | 3.00E-10 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Sunburns[28] | 2.00E-19 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Tanning[28] | 1.00E-65 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Basal cell carcinoma[29] | 4.00E-17 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Blond vs. brown hair color[30] | 2.00E-13 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Freckles[30] | 1.00E-96 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Red vs non-red hair color[30] | 2.00E-142 |
| | | rs1805007 | 16 | 89,986,117 | 16q24.3 | 0.25 | Skin sensitivity to sun[30] | 2.00E-55 |
| *TP53INP2* | rs6088580 | rs2284378 | 20 | 32,588,095 | 20q11.22 | 0.25 | Breast cancer[31] | 1.00E-08 |
| | | rs4911414 | 20 | 32,729,444 | 20q11.22 | 0.25 | Tanning[28] | 4.00E-09 |
| | | rs4911414 | 20 | 32,729,444 | 20q11.22 | 0.25 | Burning and freckling[32] | 6.00E-37 |
| | | rs4911414 | 20 | 32,729,444 | 20q11.22 | 0.25 | Freckles[32] | 8.00E-29 |
| | | rs4911414 | 20 | 32,729,444 | 20q11.22 | 0.25 | Red vs. non-red hair color[32] | 3.00E-09 |
| | | rs4911414 | 20 | 32,729,444 | 20q11.22 | 0.25 | Skin sensitivity to sun[32] | 2.00E-24 |
| | | rs910873 | 20 | 33,171,772 | 20q11.22 | 0.21 | Melanoma[33] | 1.00E-15 |
| | | rs8114671 | 20 | 33,789,142 | 20q11.22 | 0.47 | Height[14] | 1.00E-15 |
| | | rs6088765 | 20 | 33,799,280 | 20q11.22 | 0.34 | Ulcerative colitis[17] | 2.00E-08 |

* LD between published and index SNPs**.**

**Supplementary Table 8**. Study sample characteristics, African ancestry meta-analysis**.**

| Study | Sample Size | European Ancestry % - change to median with 25/75$^{th}$ percentiles | Women % | Mean age (years) | Mean eGFRcrea (ml/min/1.73 m$^2$) | CKD % |
|---|---|---|---|---|---|---|
| ARIC | 2786 | 15.3 (10.7, 22.1) | 63.1 | 53.3 | 100 | 3.7 |
| CARDIA | 821 | 16.7 (12.2, 23.2) | 61.1 | 39.4 | 111 | 0.9 |
| CHS | 728 | 20.6 (12.4, 32.7) | 62.8 | 72.9 | 81 | 18.4 |
| JHS | 2135 | 15.7 (11.8, 21.1) | 60.8 | 50 | 101 | 4.2 |
| MESA | 1640 | 18.8 (11.5, 29.7) | 54.8 | 62.2 | 87 | 8.6 |
| GENOA | 1217 | 12.6 (7.2, 18.9) | 71.7 | 63.2 | 88 | 13.0 |
| HANDLS | 989 | 16.1 (11.2, 22.0) | 55.0 | 48.4 | 121 | 5.3 |
| Health ABC | 1139 | 22.4 (12.2, 32.6) | 57.2 | 73.4 | 76 | 17.1 |
| HUFS | 1013 | 19.7 (14.3, 27.0) | 58.8 | 48.3 | 104 | 4.9 |
| IPM | 712 | 12.5 (7.1, 19.5) | 60.0 | 59.7 | 76 | 36.4 |
| SIGNET-Sea Islands | 1275 | 7.0 (4.3, 11.7) | 77.1 | 53.7 | 106 | 9.6 |
| SIGNET-REGARDS | 2385 | 14.8 (9.0, 22.9) | 63.7 | 63 | 100 | 10.0 |

Abbreviations: eGFRcrea: estimated glomerular filtration rate by serum creatinine, CKD: chronic kidney disease.

**Supplementary Table 9.** Evaluation of replicated SNPs among individuals of Asian (AGEN) and the African Ancestry Renal meta-analysis**.**

| Locus name | SNPID | Eff. All. | Non Eff. All. | AGEN Consortium[19] | | | | African Ancestry Renal Meta-Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Eff. All. Freq. | Beta (SE) | P-value | N | Ref. all freq. | Beta (SE) | P-value |
| *SYPL2* | rs12136063 | A | G | 36,057 | 0.90 | -0.0004 (0.0021) | 0.85 | 16,349 | 0.32 | 0.0049 (0.0036) | 0.16 |
| *CACNA1S* | rs3850625 | A | G | 41,963 | 0.09 | -0.0012 (0.0019) | 0.53 | 11,194 | 0.02 | 0.0127 (0.0135) | 0.35 |
| *SDCCAG8* | rs2802729 | A | C | 42,296 | 0.29 | -0.0007 (0.0009) | 0.42 | 15,461 | 0.47 | -0.0007 (0.0036) | 0.85 |
| *LRP2* | rs4667594 | A | T | 40,415 | 0.13 | -0.0015 (0.0013) | 0.24 | 15,417 | 0.61 | -0.0016 (0.0034) | 0.63 |
| *IGFBP5* | rs2712184 | A | C | 40,415 | 0.51 | -0.0025 (0.0008) | 0.0024 | 16,210 | 0.48 | -0.0023 (0.0034) | 0.50 |
| *WNT7A* | rs6795744 | A | G | 42,296 | 0.11 | -0.0001 (0.0016) | 0.94 | 16,420 | 0.21 | 0.0032 (0.0043) | 0.46 |
| *SKIL* | rs9682041 | T | C | 42,296 | 0.91 | -0.0047 (0.0018) | 0.0074 | 15,460 | 0.75 | -0.0005 (0.0041) | 0.91 |
| *ETV5* | rs10513801 | T | G | 37,250 | 0.93 | 0.0006 (0.0026) | 0.82 | 14,243 | 0.95 | -0.0006 (0.0100) | 0.95 |
| *NFKB1* | rs228611 | A | G | 42,296 | 0.52 | -0.0001 (0.0008) | 0.88 | 16,450 | 0.24 | 0.0042 (0.0040) | 0.29 |
| *ZNF204* | rs7759001 | A | G | 40,415 | 0.62 | -0.0005 (0.0008) | 0.56 | 16,435 | 0.87 | 0.0044 (0.0050) | 0.38 |
| *UNCX* | rs10277115 | A | T | 40,415 | 0.65 | 0.0066 (0.0011) | 7.30E-10 | 11,801 | 0.70 | 0.0059 (0.0060) | 0.32 |
| *KBTBD2* | rs3750082 | A | T | 39,440 | 0.32 | 0.0012 (0.0009) | 0.19 | 15,461 | 0.67 | 0.0070 (0.0039) | 0.07 |
| *RNF32* | rs6459680 | T | G | 40,415 | 0.62 | -0.0005 (0.0009) | 0.56 | 16,435 | 0.54 | 0.0049 (0.0034) | 0.15 |
| *A1CF* | rs10994860 | T | C | 41,963 | 0.10 | 0.0014 (0.0017) | 0.42 | 15,461 | 0.22 | 0.0060 (0.0045) | 0.18 |
| *KCNQ1* | rs163160 | A | G | 40,415 | 0.83 | 0.0022 (0.0011) | 0.04 | 16,467 | 0.93 | 0.0053 (0.0067) | 0.43 |
| *AP5B1* | rs4014195 | G | C | 40,415 | 0.20 | -0.0040 (0.0010) | 0.00012 | 15,297 | 0.22 | -0.0014 (0.0042) | 0.74 |
| *TSPAN9* | rs10491967 | A | G | 40,415 | 0.45 | -0.0013 (0.0008) | 0.13 | 15,460 | 0.40 | 0.0072 (0.0043) | 0.09 |
| *PTPRO* | rs7956634 | T | C | 40,415 | 0.68 | -0.0020 (0.0009) | 0.03 | 16,403 | 0.50 | -0.0082 (0.0033) | 0.01 |
| *INHBC* | rs1106766 | T | C | 42,296 | 0.11 | 0.0003 (0.0015) | 0.85 | 16,415 | 0.10 | -0.0008 (0.0057) | 0.89 |
| *DPEP1* | rs164748 | G | C | 39,164 | 0.08 | 0.0016 (0.0024) | 0.49 | 16,471 | 0.11 | 0.0025 (0.0055) | 0.65 |
| *NFATC1* | rs8091180 | A | G | 40,415 | 0.83 | -0.0004 (0.0011) | 0.69 | 3,838 | 0.20 | -0.0021 (0.0101) | 0.84 |
| *SIPA1L3* | rs11666497 | T | C | 40,415 | 0.12 | -0.0027 (0.0013) | 0.03 | 16,422 | 0.07 | 0.0023 (0.0064) | 0.72 |
| *TP53INP2* | rs6088580 | G | C | 36,275 | 0.64 | 0.0007 (0.0009) | 0.45 | NA | NA | NA | NA |
| *BCAS1* | rs17216707 | T | C | 35,492 | 0.86 | -0.0012 (0.0018) | 0.52 | 15,399 | 0.94 | -0.0049 (0.0073) | 0.50 |

**Supplementary Table 10**. Transethnic meta-analysis of CKDGen and the African Ancestry Renal Meta-Analysis**.***

| SNPID | Locus name | Chr. | Effect Allele | Non-Effect Allele | log10BF# | Posterior Probability |
|---|---|---|---|---|---|---|
| rs17216707 | *BCAS1* | 20 | T | C | 11.63 | 0.038 |
| rs4014195 | *AP5B1* | 11 | C | G | 9.66 | 0.025 |
| rs10994860 | *A1CF* | 10 | T | C | 9.52 | 0.025 |
| rs7956634 | *PTPRO* | 12 | T | C | 9.07 | 0.015 |
| rs10277115 | *UNCX* | 7 | A | T | 8.84 | 0.023 |
| rs228611 | *NFKB1* | 4 | A | G | 7.65 | 0.07 |
| rs6088580 | *TP53INP2* | 20 | C | G | 7.44 | 0.021 |
| rs163160 | *KCNQ1* | 11 | A | G | 7.38 | 0.026 |
| rs3850625 | *CACNA1S* | 1 | A | G | 7.34 | 0.046 |
| rs6795744 | *WNT7A* | 3 | A | G | 7.04 | 0.046 |
| rs10491967 | *TSPAN9* | 12 | A | G | 6.93 | 0.725 |
| rs2712184 | *IGFBP5* | 2 | A | C | 6.72 | 0.021 |
| rs3750082 | *KBTBD2* | 7 | A | T | 6.65 | 0.01 |
| rs6459680 | *RNF32* | 7 | T | G | 6.42 | 0.701 |
| rs12136063 | *SYPL2* | 1 | A | G | 6.18 | 0.012 |
| rs2802729 | *SDCCAG8* | 1 | A | C | 6.00 | 0.021 |
| rs10513801 | *ETV5* | 3 | T | G | 5.88 | 0.03 |
| rs164748 | *DPEP1* | 16 | C | G | 5.83 | 0.045 |
| rs4667594 | *LRP2* | 2 | A | T | 5.72 | 0.027 |
| rs11666497 | *SIPA1L3* | 19 | T | C | 5.72 | 0.031 |
| rs1106766 | *INHBC* | 12 | T | C | 5.56 | 0.053 |
| rs7759001 | *ZNF204* | 6 | A | G | 5.23 | 0.051 |
| rs9682041 | *SKIL* | 3 | T | C | 5.04 | 0.032 |
| rs8091180 | *NFATC1* | 18 | A | G | 4.87 | 0.044 |

*The analysis was performed using the MANTRA (Meta-Analysis of Trans-ethnic Association studies) software.[34] The posterior probability is a measure of heterogeneity of allelic effects across the individual studies.

#$Log_{10}$ Bayes Factor

**Supplementary Table 11**. SNP associations with transcript expression.*

| *Locus name; index SNP* | *eSNP* | | | | | | | | | *Best eSNP* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *eSNP rsID* | *Dist. index SNP* | *$r^2$* | *eQTL tissue[REF]* | *P-value* | *Chr* | *position* | *Probe** | *Transcript*** | *Best eSNP rsID* | *P-value* | *$r^2$ to eSNP* | *$r^2$ to index SNP* |
| *SYPL2* rs12136063 | rs12136063 | 0 | 1.00 | Prefrontal cortex - all samples[35] | 1.3E-05 | 1 | 109,815,693 | 10031920561 | SYPL2 | rs12136063 | 1.3E-05 | Same | Same |
| | rs10494040 | 1,562 | 1.00 | SubCutAdipose[36] | 6.5E-50 | 1 | 109,817,255 | 10031920561 | SYPL2 | rs10494040 | 6.5E-50 | Same | 0.96 |
| | rs10494040 | 1,562 | 1.00 | Liver[36] | 5.4E-47 | 1 | 109,817,255 | 10031920561 | SYPL2 | rs10494040 | 5.4E-47 | Same | 0.96 |
| | rs10857787 | 3,881 | 1.00 | Liver[37] | 2.9E-35 | 1 | 109,811,812 | | SYPL2 | rs10857787 | 2.9E-35 | Same | 0.96 |
| | rs4970767 | 1,013 | 1.00 | Liver (UChicago)[38] | 8.9E-16 | 1 | 109,816,706 | A_23_P317200 | ATXN7L2 | rs4970767 | 8.9E-16 | Same | 0.96 |
| | rs10494040 | 1,562 | 1.00 | OmentalAdipose[36] | 9.4E-13 | 1 | 109,817,255 | 10031920561 | SYPL2 | rs10494040 | 9.4E-13 | Same | 0.96 |
| | rs10494040 | 1,562 | 1.00 | Liver[39] | 1.1E-12 | 1 | 109,817,255 | | SYPL2 | rs10494040 | 1.1E-12 | Same | 0.96 |
| | rs4970767 | 1,013 | 1.00 | Liver (UWash)[38] | 3.3E-02 | 1 | 109,816,706 | 5360451 | ATXN7L2 | rs4970767 | 3.3E-02 | Same | 0.96 |
| | rs4970729 | 34,968 | 0.92 | Liver[36] | 2.3E-24 | 1 | 109,780,725 | 10025910902 | PSMA5 | rs4970729 | 2.3E-24 | Same | 0.89 |
| | rs12073497 | 39,720 | 0.92 | Liver[36] | 6.2E-09 | 1 | 109,775,973 | 10023805980 | Contig42599_RC | rs12073497 | 6.2E-09 | Same | 0.89 |
| | rs12073497 | 39,720 | 0.92 | Visual cortex - all samples[35] | 3.1E-06 | 1 | 109,775,973 | 10031920561 | SYPL2 | rs12073497 | 3.1E-06 | Same | 0.89 |
| | rs4970729 | 34,968 | 0.92 | Cerebellum - all samples[35] | 1.1E-05 | 1 | 109,780,725 | 10025932473 | AMIGO1 | rs4970729 | 1.1E-05 | Same | 0.89 |
| | rs2781553 | 12,819 | 0.85 | Liver[36] | 4.8E-05 | 1 | 109,828,512 | 10025909878 | PRPF38B | rs2781553 | 4.8E-05 | Same | 0.85 |
| *SDCCAG8* rs2802729 | rs2802723 | 3,451 | 1.00 | Periph artery plaque‡ | 4.1E-07 | 1 | 241,564,935 | 100142973_TGI_at | SDCCAG8 | rs2802723 | 4.1E-07 | Same | 1.00 |
| | rs2490395 | 42,841 | 0.83 | Blood[40] | 9.2E-06 | 1 | 241,525,545 | 460458 | SDCCAG8 | rs2490395 | 9.2E-06 | Same | 0.83 |
| | rs2484639 | 39,396 | 0.81 | Visual cortex - all samples[35] | 3.2E-07 | 1 | 241,528,990 | 10025912019 | SDCCAG8 | rs2484639 | 3.2E-07 | Same | 0.80 |
| *NFKB1* rs228611 | rs228611 | 0 | 1.00 | LCL MuTHER [41] | 1.6E-19 | 4 | 103,780,757 | ILMN_1800733 | MANBA | rs228611 | 1.6E-19 | Same | Same |
| | rs228611 | 0 | 1.00 | Prefrontal cortex (Huntington's)[35] | 1.4E-08 | 4 | 103,780,757 | 10025907439 | MANBA | rs228611 | 1.4E-08 | Same | Same |
| | rs228611 | 0 | 1.00 | Lymphocytes[42] | 2.0E-08 | 4 | 103,780,757 | | MANBA | rs228611 | 2.0E-08 | Same | Same |
| | rs228611 | 0 | 1.00 | Visual cortex (Alzheimer's)[35] | 5.6E-05 | 4 | 103,780,757 | 10025907439 | MANBA | rs228611 | 5.6E-05 | Same | Same |
| | rs228611 | 0 | 1.00 | Cerebellum - all samples[35] | 6.7E-02 | 4 | 103,780,757 | 10025907439 | MANBA | rs228611 | 6.7E-02 | Same | Same |
| | rs909349 | 5,393 | 0.97 | Monocytes[43] | 2.5E-121 | 4 | 103,775,364 | | MANBA | rs909349 | 2.5E-121 | Same | 0.97 |
| | rs7665090 | 10,106 | 0.97 | OmentalAdipose[36] | 6.5E-42 | 4 | 103,770,651 | 10025907439 | MANBA | rs7665090 | 6.5E-42 | Same | 0.97 |
| | rs228611 | 0 | 1.00 | Blood[40] | 1.3E-30 | 4 | 103,780,757 | 4230168 | MANBA | rs7665090 | 3.9E-37 | 0.97 | 0.97 |
| | rs7665090 | 10,106 | 0.97 | Prefrontal cortex - all samples[35] | 2.4E-26 | 4 | 103,770,651 | 10025907439 | MANBA | rs7665090 | 2.4E-26 | Same | 0.97 |

**Supplementary Table 11** (continued).

| *Locus name; index SNP* | *eSNP* | | | | | | | | | *Best eSNP* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *eSNP rsID* | *Dist. index SNP* | *$r^2$* | *eQTL tissue[REF]* | *P-value* | *Chr* | *position* | *Probe** | *Transcript*** | *Best eSNP rsID* | *P-value* | *$r^2$ to eSNP* | *$r^2$ to index SNP* |
| *NFKB1* rs228611 | rs228614 | 16,928 | 0.91 | Blood[40] | 2.0E-22 | 4 | 103,797,685 | 4230168 | MANBA | rs7665090 | 3.9E-37 | 0.87 | 0.97 |
| | rs2866413 | 4,632 | 0.97 | Prefrontal cortex - all samples[35] | 5.8E-17 | 4 | 103,776,125 | 10025907439 | MANBA | rs7665090 | 2.4E-26 | 1 | 0.97 |
| | rs2866413 | 4,632 | 0.97 | Visual cortex - all samples[35] | 5.8E-08 | 4 | 103,776,125 | 10025907439 | MANBA | rs2866413 | 5.8E-08 | Same | 0.97 |
| | rs228614 | 16,928 | 0.91 | Blood[44] | 2.1E-05 | 4 | 103,797,685 | HSG00228144 | MANBA | rs228614 | 2.1E-05 | Same | 0.91 |
| | rs404574 | 21,499 | 0.90 | SubCutAdipose MuTHER[41] | 1.7E-14 | 4 | 103,802,256 | ILMN_1800733 | MANBA | rs404574 | 1.7E-14 | Same | 0.84 |
| | rs7674640 | 20,929 | 0.81 | Lung[45] | <2E-16 | 4 | 103,759,828 | 100150393_TGI_at | CISD2 | rs7674640 | <2E-16 | Same | 0.81 |
| *ZNF204* rs7759001 | rs7759001 | 0 | 1.00 | Intestine normal ileum[46] | 1.3E-10 | 6 | 27,341,409 | | ZNF391 | rs7759001 | 1.3E-10 | Same | Same |
| | rs7759001 | 0 | 1.00 | Cerebellum - normal samples[35] | 5.5E-09 | 6 | 27,449,388 | 10025913649 | BC035154 | rs7759001 | 5.5E-09 | Same | Same |
| | rs2143062 | 12,443 | 1.00 | Cerebellum (Alzheimer's)[35] | 1.6E-11 | 6 | 27,461,831 | 10025913649 | BC035154 | rs2143062 | 1.6E-11 | Same | 1.00 |
| | rs2143062 | 12,443 | 1.00 | Prefrontal cortex (Huntington's)[35] | 1.4E-05 | 6 | 27,461,831 | 10025913649 | BC035154 | rs2143062 | 1.4E-05 | Same | 1.00 |
| | rs9368508 | 19,561 | 1.00 | Cerebellum (Huntington's)[35] | 3.4E-06 | 6 | 27,429,827 | 10025913649 | BC035154 | rs9368508 | 3.4E-06 | Same | 0.95 |
| | rs10755644 | 4,696 | 1.00 | SubCutAdipose[36] | 7.0E-05 | 6 | 27,444,692 | 10025933640 | ZNF391 | rs10755644 | 7.0E-05 | Same | 0.90 |
| | rs10807021 | 15,516 | 0.95 | OmentalAdipose[36] | 1.5E-08 | 6 | 27,464,904 | 10025913649 | BC035154 | rs10807021 | 1.5E-08 | Same | 0.86 |
| | rs4713086 | 9,037 | 0.95 | Periph artery plaque‡ | 1.9E-07 | 6 | 27,458,425 | 100139132_TGI_at | BC035154 | rs4713086 | 1.9E-07 | Same | 0.86 |
| | rs980963 | 19,528 | 0.86 | Cerebellum - all samples[35] | 2.3E-05 | 6 | 27,468,916 | 10025933640 | ZNF391 | rs980963 | 2.3E-05 | Same | 0.86 |
| | rs10807020 | 15,493 | 0.95 | Cerebellum - normal samples[35] | 5.3E-05 | 6 | 27,464,881 | 10025907341 | NM_178534 | rs10807020 | 5.3E-05 | Same | 0.86 |
| | rs10807021 | 15,516 | 0.95 | Visual cortex - all samples[35] | 1.3E-03 | 6 | 27,464,904 | 10025908866 | ZNF184 | rs10807021 | 1.3E-03 | Same | 0.86 |
| *KBTBD2* rs3750082 | rs6462431 | 15,512 | 0.93 | Blood[40] | 2.3E-38 | 7 | 32,901,964 | 4920372 | KBTBD2 | rs6462431 | 2.3E-38 | Same | 0.89 |
| | rs3750082 | 0 | 1.00 | LCL asthmatics [47] | 8.1E-17 | 7 | 32,886,452 | 212447_at | KBTBD2 | rs7785065 | 8.1E-17 | 0.89 | 0.89 |
| | rs3750082 | 0 | 1.00 | LCL MuTHER[41] | 1.1E-06 | 7 | 32,886,452 | ILMN_1784540 | KBTBD2 | rs13230763 | 8.3E-08 | 0.80 | 0.89 |
| | rs2392152 | 19,378 | 0.89 | Liver[37] | 2.0E-10 | 7 | 32,867,074 | | HSS00226368 | rs2392152 | 2.0E-10 | Same | 0.85 |
| | rs4723221 | 34,280 | 0.82 | Lung[45] | 6.4E-08 | 7 | 32,920,732 | 100132413_TGI_at | KBTBD2 | rs4723221 | 6.4E-08 | Same | 0.82 |

**Supplementary Table 11** (continued).

| *Locus name; index SNP* | *eSNP* | | | | | | | | | *Best eSNP* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *eSNP rsID* | *Dist. index SNP* | *$r^2$* | *eQTL tissue[REF]* | *P-value* | *Chr* | *position* | *Probe** | *Transcript*** | *Best eSNP rsID* | *P-value* | *$r^2$ to eSNP* | *$r^2$ to index SNP* |
| *AP5B1* rs4014195 | rs11227281 | 10,264 | 1.00 | Intestine -normal ileum[46] | 3.8E-05 | 11 | 65,496,558 | | EIF1AD | rs11227281 | 3.8E-05 | Same | 1.00 |
| | rs11604451 | 44,888 | 1.00 | LCL (Degner - DNAse QTLs)[48] | 2.9E-04 | 11 | 65,308,286 | | DNAse QTL 65308500-65308600 | rs11604451 | 2.9E-04 | Same | 1.00 |
| *PTPRO* rs7956634 | rs2193172 | 11,148 | 1.00 | Liver (UChicago)[38] | 6.6E-03 | 12 | 15,223,609 | A_23_P204304 | PTPRO | rs2193172 | 6.6E-03 | Same | 1.00 |
| *INHBC* rs1106766 | rs1106766 | 0 | 1.00 | ER+ breast tumor cells[49] | 7.7E-06 | 12 | 56,095,723 | | GLS2 | rs11614506 | 3.4E-07 | 0.80 | 0.80 |
| *DPEP1* rs164748 | rs164749 | 68 | 1.00 | Liver[37] | 2.5E-09 | 16 | 88,235,725 | | C16orf55 (SPATA33) | rs164749 | 2.5E-09 | Same | 1.00 |
| | rs460879 | 4,597 | 1.00 | Prefrontal cortex (Huntington's)[35] | 3.0E-08 | 16 | 88,240,390 | 10025907286 | C16orf55 (SPATA33) | rs460879 | 3.0E-08 | Same | 1.00 |
| | rs460879 | 4,597 | 1.00 | OmentalAdipose[36] | 2.7E-06 | 16 | 88,240,390 | 10025902450 | CHMP1A | rs460879 | 2.7E-06 | Same | 1.00 |
| | rs154657 | 196 | 1.00 | Periph artery plaque‡ | 1.7E-05 | 16 | 88,235,597 | 100143418_TGI_at | SPATA2L | rs154657 | 1.7E-05 | Same | 1.00 |
| | rs460879 | 4,597 | 1.00 | Cerebellum (Huntington's)[35] | 3.1E-05 | 16 | 88,240,390 | 10025902450 | CHMP1A | rs460879 | 3.1E-05 | Same | 1.00 |
| | rs459920 | 22,535 | 0.97 | OmentalAdipose[36] | 3.7E-44 | 16 | 88,258,328 | 10025907286 | C16orf55 (SPATA33) | rs459920 | 3.7E-44 | Same | 0.97 |
| | rs459920 | 22,535 | 0.97 | SubCutAdipose[36] | 1.2E-30 | 16 | 88,258,328 | 10025907286 | C16orf55 (SPATA33) | rs459920 | 1.2E-30 | Same | 0.97 |
| | rs459920 | 22,535 | 0.97 | Cerebellum -all samples[35] | 1.8E-30 | 16 | 88,258,328 | 10025907286 | C16orf55 (SPATA33) | rs459920 | 1.8E-30 | Same | 0.97 |
| | rs459920 | 22,535 | 0.97 | Prefrontal cortex - all samples[35] | 4.8E-23 | 16 | 88,258,328 | 10025907286 | C16orf55 (SPATA33) | rs459920 | 4.8E-23 | Same | 0.97 |
| | rs459920 | 22,535 | 0.97 | Liver[36] | 2.1E-21 | 16 | 88,258,328 | 10025907286 | C16orf55 (SPATA33) | rs459920 | 2.1E-21 | Same | 0.97 |
| | rs459920 | 22,535 | 0.97 | Visual cortex -all samples[35] | 2.7E-17 | 16 | 88,258,328 | 10025907286 | C16orf55 (SPATA33) | rs459920 | 2.7E-17 | Same | 0.97 |
| | rs2115401 | 32,317 | 0.97 | Peripheral artery plaque‡ | 3.6E-07 | 16 | 88,268,110 | 100138862_TGI_at | C16orf55 (SPATA33) | rs2115401 | 3.6E-07 | Same | 0.97 |
| | rs467035 | 31,993 | 0.97 | Peripheral artery plaque‡ | 6.0E-06 | 16 | 88,267,786 | 100131451_TGI_at | SNAI3 | rs467035 | 6.0E-06 | Same | 0.97 |
| | rs258319 | 23,732 | 0.97 | Temporal cortex[50] | 4.8E-05 | 16 | 88,259,525 | ILMN_1759261 | C16orf55 (SPATA33) | rs258319 | 4.8E-05 | Same | 0.97 |
| | rs2115401 | 32,317 | 0.97 | Liver (UWash)[38] | 1.7E-04 | 16 | 88,268,110 | 1300411 | C16orf55 (SPATA33) | rs2115401 | 1.7E-04 | Same | 0.97 |

**Supplementary Table 11** (continued).

| *Locus name; index SNP* | *eSNP* | | | | | | | | | *Best eSNP* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *eSNP rsID* | *Dist. index SNP* | *$r^2$* | *eQTL tissue$^{REF}$* | *P-value* | *Chr* | *position* | *Probe** | *Transcript*** | *Best eSNP rsID* | *P-value* | *$r^2$ to eSNP* | *$r^2$ to index SNP* |
| *DPEP1* rs164748 | rs2115401 | 32,317 | 0.97 | Liver (UChicago)[38] | <1e-16 | 16 | 88,268,110 | A_24_P159335 | C16orf55 (SPATA33) | rs2115401 | <1e-16 | Same | 0.97 |
| | rs459920 | 22,535 | 0.97 | Liver (UChicago)[38] | <1e-16 | 16 | 88,258,328 | A_23_P106694 | CHMP1A | rs459920 | <1e-16 | Same | 0.97 |
| *TP53INP2* rs6088580 | rs2273684 | 244,713 | 0.94 | Blood[40] | 7.6E-08 | 20 | 32,993,427 | 7150537 | ACSS2 | rs2273684 | 7.6E-08 | Same | 0.94 |
| | rs2273684 | 244,713 | 0.94 | Blood[40] | 1.5E-06 | 20 | 32,993,427 | 2680161 | GSS | rs2273684 | 1.5E-06 | Same | 0.94 |
| | rs6059909 | 145,362 | 0.84 | Lymphocytes[51] | 2.2E-03 | 20 | 32,603,352 | GI_31563517-A | MAP1LC3A | rs6059909 | 2.2E-03 | Same | 0.81 |

* Expression QTL results were identified for our index SNPs or their proxies within the following dataset sources: whole blood samples,[40, 44] Epstein-Barr transformed B-lymphoblastoid cell lines (LCL) from population samples,[41, 42, 47] DNase-I QTLs in LCLs,[48] fresh lymphocytes,[51] peripheral blood monocytes,[43] ER+ breast cancer tumor cells,[49] omental and/or subcutaneous adipose,[36, 41] peripheral artery plaque intestine,[46] lung,[45] brain,[35, 50] and liver.[36-39]

‡ Unpublished (Emilsson)

**Supplementary Table 12**. Background information on novel replicated loci**.**

| SNPID (Locus name) | Evidence from functional databases | | Gene prioritized for functional work | Description of Genes in each Region* |
|---|---|---|---|---|
| | Source | Gene | | |
| rs228611 (*NFKB1*) | **eSNP** | *MANBA* | *NFKB1* closest gene | *MANBA* encodes beta-mannosidase, a lysosomal enzyme that catalyzes the final exoglycosidase step in the degradation pathway for N-linked oligosaccharide moieties of glycoproteins (RefSeq). Rare mutations have been identified as the cause for beta-mannosidosis (OMIM #248510). A mouse model has linked *MANBA* to lysosomal storage disease in multiple organs, including the kidney.[52] *NFKB1* encodes a pleiotropic transcription factor that is present in almost all cell types and is the endpoint of a series of signal transduction events that are initiated by a vast array of stimuli related to many biological processes such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis (RefSeq). |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs7759001 (*ZNF204*) | **eSNP** | NA | NO | ZNF204 is known as a transcribed pseudogene (RefSeq). ZNF391 and ZNF184 are two neighboring zinc finger protein-coding genes (RefSeq). Little is known about other nearby genes in the region. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs1106766 (*INHBC*) | **eSNP** | NO | NO | *R3HDM2* encodes a protein with R3H domain. *INHBC* encodes the beta C chain of inhibin, which forms heterodimers with beta A and beta B subunits. Inhibins are involved in hormonal secretion and growth and differentiation of various cell types (RefSeq). *GLI1* encodes a transcription factor that is activated by the sonic hedgehog signal transduction cascade that regulates stem cell proliferation (RefSeq). The hedgehog-GII pathway has been implicated in kidney fibrosis in mouse studies.[53] *ARHGAP9* encodes a member of the Rho-GAP family of GTPase activating proteins, converting them to an inactive GDP-bound state (RefSeq). |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs10513801 (*ETV5*) | **eSNP** | NA | NO | The *ETV5* gene is a ubiquitously expressed transcription factor. A role in renal development has been shown in a mouse model[54]. In humans, it has not yet been connected to kidney disease. *DGKG* encodes diacylglycerol Kinase, Gamma, a glycerol kinase that metabolizes 1,2,diacylglycerol to produce the second messenger phosphatidic acid. The transcript is expressed in kidney. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs3850625 (*CACNA1S*) | **eSNP** | NA | NO | *CACNA1S* encodes one of five subunits of the slowly inactivating L-type voltage-dependent calcium channel, which plays a role in skeletal muscle contraction. Known mutations in *CACNA1S* have been associated with susceptibility to malignant hyperthermia, hypokalemic periodic paralysis, and thyrotoxic periodic paralysis. The identified variant is a non-synonymous coding SNP at a highly conserved position (R1539C on protein level) that is predicted as damaging or pathogenic by 3 out of 4 prediction software. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs10491967 (*TSPAN9*) | **eSNP** | NA | *TSPAN9* | *TSPAN9* encodes for a member of the tetraspanin family, which assemble in complexes with additional proteins such as integrins to transduct signals. Its association to renal function is unclear; mutations in some integrins cause monogenic kidney disease, as do mutations in the gene paralog CD151. Other genes in the region have not specifically been connected to kidney disease. |
| | **GRAIL** | NO | | |
| | **DEPICT** | *TSPAN9* FDR<0.05 | | |

**Supplementary Table 12** (continued).

| SNPID (Locus name) | Evidence from functional databases | | Gene prioritized for functional work | Description of Genes in each Region* |
|---|---|---|---|---|
| | **Source** | **Gene** | | |
| rs164748 (*DPEP1*) | **eSNP** | *C16orf55* (also known as *SPATA33*) | *DPEP1* | *DPEP1* encodes dipeptidase 1, an enzyme responsible for hydrolysis of glutathione and certain types of antibiotics in the kidney membrane[55,56] and is highly expressed in the kidney and pancreas (GeneCards), but there are no studies linking this gene to kidney function. *RPL13* encodes ribosomal protein L13, a protein within the large 60S ribosomal subunit complex[57]. There are no publications linking RPL13 to the kidney or kidney function. *SNORD68* encodes small nucleolar RNA C/D box 68 a class molecules that modify other RNAs. This particular class of snoRNA is responsible for RNA methylation. There are no known connections to kidney function or disease. *SPG7* encodes paraplegin, an enzyme component of m-AAA protease (a mitochondrial enzyme responsible for degradation of malformed or misfolded proteins).[58] Mutations in the *SPG7* gene lead to monogenic forms of spastic paraplegia.[59, 60, 60, 61, 61] There are no reported studies linking *SPG7* and kidney function. *ANKRD11* encodes ankyrin repeat domain protein 11, a protein inhibiting ligand-dependent activation of transcription. Variation in *ANKRD11* can lead to KBG syndrome (a disorder with abnormal skeletal development and delay in neurological development.[62, 63, 63] No associations of *ANKRD*11 and kidney function have been published. *C16orf55* (also known as *SPATA33*) encodes spermatogenesis-associated protein 33 and is thought to be involved in spermatogenesis. No associations with kidney disease have been identified. |
| | **GRAIL** | NO | | |
| | **DEPICT** | DPEP1 FDR<0.05 | | |
| rs8091180 (*NFATC1*) | **eSNP** | NA | *NFATC1* | *NFATC1* encodes for nuclear factor of activated T-cells (cytoplasmic, calcineurin dependent 1) and is a part of a complex involved in the activation of immune response, specifically activation of the T-cell antigen receptor.[64] In rodents, *NFAT1C* is potentially involved in proximal tubules after injury[65] and activation of this nuclear factor may lead to glomeruloscerosis by mutant forms of *TRPC6* - a podocyte protein involved in maintaining the filtration barrier.[66] *NFAT*1C has not been linked with kidney function in humans. *ATP9B* encodes an ATPase, class II, type 9b - a transmembrane transporter. No association with kidney disease has been previously reported. *CTDP1* encodes the c-terminal domain of RNA polymerase II subunit A phosphatase. Variations in *CTDP1* have been associated with congenital cataracts, facial dimorphism and neuropathy in Bulgarian gypsy populations.[67] There have been no previous reports of *CTDP1* and kidney disease. |
| | **GRAIL** | *NFATC1* p=0.03 | | |
| | **DEPICT** | NO | | |
| rs11666497 (*SIPA1L3*) | **eSNP** | NA | NO | *SIPA1L3* encodes the signal-induced proliferation-associated 1 like 3 protein. There are no published reports in the literature describing this gene or its protein product. *WDR87* encodes the WD repeat-containing protein 87, a protein 2.8K amino acids in length. There are no published reports of this gene or gene product in the literature. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |

**Supplementary Table 12** (continued).

| SNPID (Locus name) | Evidence from functional databases | | Gene prioritized for functional work | Description of Genes in each Region* |
|---|---|---|---|---|
| | Source | Gene | | |
| rs4667594 (*LRP2*) | **eSNP** | NA | NO | *LRP2* encodes the megalin receptor, which plays an important role in the reabsorption of albumin and other low-molecular-weight proteins[68] along with cubilin (*CUBN*) and amnionless (*AMN*). *LRP2* mutations are associated with Donnai-Barrow and facio-oculo-acoustico-renal syndromes.[69] *DHRS9* is a protein-coding gene that encodes dehydrogenase/reductase member 9 (GeneCards). It is a 3-alpha-hydroxysteroid dehydrogenase that is responsible for the synthesis of dihydroxyprotesterone; low levels of activity with retinoids have also been identified (UCSC). There are no published studies linking this gene to kidney function. *ABCB11* belongs to the ATP-binding cassette superfamily. The protein is involved in bile salt export (www.genecards.org), and mutations are involved in familial intrahepatic cholestasis (OMIM). In addition, this gene may be involved with bile acid transport in the kidney.[70] |
| | **GRAIL** | *LRP2* p=0.0004 | | |
| | **DEPICT** | *LRP2* FDR<0.05 | | |
| rs6795744 (*WNT7A*) | **eSNP** | NA | *WNT7A* closest gene | *WNT7A* is a member of set of genes that are signaling proteins, specifically those that are involved in embryogenesis (www.genecards.org). Mutations in this gene have been associated with Fuhrmann syndrome (OMIM #228930) and the Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome (AARRS; OMIM #276820), disorders characterized by limb malformation. Wnt-7a signalling may allow for the development of sexual dimorphism via development of the mullerian ducts.[71] *TPRXL* is a homeobox gene thought to be involved in embryonic development (GeneCards). There are no published papers linking this gene to kidney function. Of the remaining genes in the region, only *XPC* has been previously linked to kidney function in the published literature. *XPC* is a DNA repair gene. Mutations result in Xeroderma pigmentosum, a disease characterized by sunlight sensitivity and early carcinomas. Mutations in *XPC* may be associated with renal cell carcinoma.[72] |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs7956634 (*PTPRO*) | **eSNP** | *PTPRO* | *PTPRO* closest gene | *RERG* belongs to the RAS superfamily and is involved with cell proliferation and tumor pathogenesis (GeneCards). *RERG* expression may be lost in kidney cancer.[73] *PTPRO* is expressed in the podocyte foot processes of the kidney; mutations in *PTPRO* are associated with autosomal-recessive nephrotic syndrome.[74] Knock-out mice display reduced eGFR but no proteinuria[75]. *EPS8 i*s an epidermal growth factor receptor pathway substrate gene (GeneCards). Eps8 proteins are involved in the organization of actin filaments.[76] |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs10277115 (*UNCX*) | **eSNP** | NA | *UNCX* (no other genes in the LD block) | *UNCX* is a transcription factor that is involved in neurogenesis and somitogenesis (GeneCards). In addition, it may be involved in differentiation of the axial skeleton (GeneCards). There is no published literature linking it to kidney function. *ZFAND2A* is a protein coding gene involved in zinc ion binding (GeneCards). It has been shown to be part of a network of genes expressed in human renal epithelial cells in response to cadium exposure, a known nephrotoxin.[77] *GPER* is a member of the G-protein coupled receptor family with a primary role of binding estrogen (GeneCards). *GPER* may mediate the effects of estrogen (but not aldosterone)[78] on the vasculature[79] including the rat kidney.[80] *GPER* binds estrogen in addition to other substances including endocrine disruptors.[81] |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |

**Supplementary Table 12** (continued).

| SNPID (Locus name) | Evidence from functional databases | | Gene prioritized for functional work | Description of Genes in each Region* |
|---|---|---|---|---|
| | **Source** | **Gene** | | |
| rs12136063 (*SYPL2*) | **eSNP** | *SYPL2* | *SYPL2* | *SYPL2* encodes synaptophysin-like 2 protein (also known as mitsugumin 29), a membrane protein involved in the communication between the transverse tubular and junctional sarcoplasmatic reticulum membranes (Entrez Gene). It is expressed in the kidney (www.proteinatlas.org). There are no publications linking this gene to kidney function. *PSMA5* encodes proteasome (prosome, macropain) subunit alpha type 5, which is a proteosome involved in the processing of MHC class I peptides (Entrez Gene) and is expressed in many tissues including the kidney (ProteinAtlas). There are no publications linking this gene to kidney function. There is no disease linked to this gene in OMIM. *ATXN7L2* encodes for ataxin 7-like 2 protein (GeneCards), which is expressed in several tissues including the kidney (ProteinAtlas). There is no publication linking this gene to kidney function. *AMIGO1* encodes adhesion molecule with Ig-like domain 1, which is part of a family of transmembrane proteins involved in axon tract development.[82] It is expressed in the kidney. *CELSR2* encodes cadherin EGF LAG seven-pass G-type receptor 2, which is a member of the flamingo subfamily cadherins which does not interact with catenins (Entrez Gene). It is a plasma membrane protein postulated to be involved in contact-mediated communication and expressed in many tissues including the kidney. |
| | **GRAIL** | NO | | |
| | **DEPICT** | *SYPL2* FDR<0.05 | | |
| rs2802729 (*SDCCAG8*) | **eSNP** | *SDCCAG8* | NO | *SDCCAG8* encodes serologically defined colon cances antigen 8, a centrosome associated protein involved in interphase and mitosis (Entrez Gene). Truncating mutations cause Senior-Loken syndrome 7 (OMIM #613615), an autosomal recessive ciliopathy with nephronophthisis and Leber congenital amaurosis. *CEP170* encodes centrosomal protein 170kDa, which is the major microtubule-organizing center in animals (Entrez Gene). It is expressed in several tissues including the kidney, but has not been linked to kidney function in any publication. *AKT3* encodes v-akt murine thymoma viral oncogene homolog 3, which is a kinase regulating cell signaling in response to insulin and rowth factors; it is stimulated by PDGF, insulin and IGF-1 (Entrez Gene). It shows low-level expression in the kidney (ProteinAtlas). Rare mutations cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH, OMIM #603387), which does not show organ involvement beyond central nervous defects. There are no publications linking this gene to kidney function. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs17216707 (*BCAS1*) | **eSNP** | NA | *BCAS1* but no fish orthologs | *BCAS1* encodes breat carcinoma amplified sequence 1, which has been implicated as a breast cancer oncogene (Entrez Gene). There is no expression in the kidney (ProteinAtlas). *CYP24A1* encodes cytochrome P450, family 24, subfamily A, polypeptide 1, which initiates the degradation of 1,25 hydrox-Vitamin D3, thus regulating calcium homeostasis (Entrez Gene). Rare mutations in this gene cause infantile hypercalcemia (OMIM #143880). *CYP24A1* is expressed in the kidney. *PFDN4* encodes prefoldin subunit 4, which is part of a molecular chaperone complex needed for correct folding of newly synthesised polypeptides (Entrez Gene). There are no publications linking *PFDN4* to kidney function. *SUMO1P1* encodes *SUMO1* (small ubiquitin-like modifier 1) pseudogene 1 (Entrez Gene); *SUMO1* is part of a post-translational modification system regulating NFKB under high glucose conditions in kidney mesangial cells;[83] sumoylation protects from oxidative stress.[84] There is no publication linking *SUMO1P1* to kidney function. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |

**Supplementary Table 12** (continued).

| SNPID (Locus name) | Evidence from functional databases | | Gene prioritized for functional work | Description of Genes in each Region* |
|---|---|---|---|---|
| | **Source** | **Gene** | | |
| rs3750082 (*KBTBD2*) | **eSNP** | *KBTBD2* | *KBTBD2* | *AVL9* plays a role in late exocytic transport,[85] at the level of the Golgi.[86] This gene has not formally been associated with kidney function in the published literature. *LSM5* is a Sm-like protein that plays a role in pre-mRNA splicing (GeneCards). It has not previously been linked to kidney function in the published literature. There is little known about *KBTBD2*, and no published literature linking it to kidney function. There are several other genes in the region. |
| | **GRAIL** | NO | | |
| | **DEPICT** | *KBTBD2* FDR<0.05 | | |
| rs6088580 (*TP53INP2*) | **eSNP** | NO | NO | *TP53INP2* regulates both transcription and autophagy (UCSC). It is a scaffold protein that interacts with *VMP1*.[87] It has not been formally linked to kidney function in the literature. There are dozens of additional genes in the region. |
| | **GRAIL** | NO | | |
| | **DEPICT** | *ACSS2* and *NCOA6* FDR<0.05 | | |
| rs6459680 (*RNF32*) | **eSNP** | NA | NO | *RNF32* plays a role in spermatogenesis. The gene has not previously been identified in associaiton with kidney function. *LMBR1* plays a role in limb malformation, which may occur via altered Sonic hedgehog signaling. The gene has not been connected to kidney function or disease. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs4014195 (*AP5B1*) | **eSNP** | NA | *AP5B1* but no existing Morpholino | *KAT5* encodes for K(Lysine) acetyltransferase 5, which is important in transcriptional regulation. It has not been previously identified in association with kidney function. OVOL1 encodes for a transcription factor. *OVOL1* deficient mice of C57BL/6 background show increased perinatal lethality and other abnomalities, including cystic kidneys.[88] |
| | **GRAIL** | NO | | |
| | **DEPICT** | *AP5B1* FDR<0.05 | | |
| rs2712184 (*IGFBP5*) | **eSNP** | NA | NO | *IGFBP5* (insulin-like growth factor binding protein 5) is a protein-coding gene that either induces or suppresses cell proliferation. *IGFBP5* participates in cellular pathways of adaptation to hypertonicity in renal medulla under TonEBP control.[89] *IGFBP2* (insulin-like growth factor binding protein 2, 36kDA) regulates cell growth by enhancing or suppressing IGF bioavailability. RNA and protein are ubiquitously expressed. IGFBP2 is the most expressed among IGF binding proteins, particularly in glomerular mesangial cells where it is controlled by angiotensin and glucose concentrations.[90] *TNP1* (transition protein 1) is a protein-coding gene. In the course of spermiogenesis, *TNP1* is a spermatid-specific product that replaces histone and is itself replaced in the mature sperm by protamines. It is expressed in testis. There is no published literature relating this gene or its protein product to kidney function. |
| | **GRAIL** | NO | | |
| | **DEPICT** | NO | | |
| rs10994860 (*A1CF*) | **eSNP** | NA | *A1CF* | *A1CF* is a protein coding gene that mediates the deamination of apolipoprotein B mRNA through a multi-componenent enzyme complex including *APOBEC-1* and a complementation factor coded by *A1CF* gene. It is expressed in the gastrointestinal tract, liver, pancreas, brain and kidneys. One publication[20] links this gene to kidney reabsorption of urate (elevated serum urate concentrations). ASAH2B (N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2B) is a protein-coding gene. Ceramidases are a group of enzymes which catalyze the hydrolysis of ceramides to produce sphingosine but ASAH2B lacks the active site and therefore could be catalytically inactive. No publications link this gene to kidney function. *PRKG1* encodes the soluble alpha and I beta1 isoforms of the cGMP dependent protein kinase, involved in the regulation of cardiovascular and neuronal functions, smooth muscle relaxation, platelet aggregation, and in cell growth by modulating cellular calcium. |
| | **GRAIL** | NO | | |
| | **DEPICT** | *A1CF* FDR<0.05 | | |

**Supplementary Table 12** (continued).

| SNPID (Locus name) | Evidence from functional databases | | Gene prioritized for functional work | Description of Genes in each Region* |
|---|---|---|---|---|
| | **Source** | **Gene** | | |
| rs9682041 (*SKIL*) | **eSNP** | NA | *SKIL* | The protein encoded by SKI-like oncogene is a component of the SMAD pathway, that has a regulatory role on the cell division and differentiation through TGFß. RNA and protein are expressed in most human tissues except pancreas. *SKIL* is implicated in ubiquitin dependent tubulointerstitial fibrosis along with TGFbeta1.[91] Claudin 11 is a member of the claudin family of tight junction associated proteins. The protein encoded by this gene is a major component of the central nervous system (CNS) myelin and plays an important role in regulating proliferation and migration of oligodendrocytes. RNA and protein are expressed in Sertoli cells in testis and oligodendrocytes in the CNS. CLDN11 Claudin family is differentially expressed in tight junctions of human cortical nephron and influences pathologies involving abnormalities of absorption.[92] Its expression is significantly unregulated in genetic model of polycystic kidney in early stages.[93] RNA is expressed in cerebral cortex, while the protein is strongly expressed in hyppocampus and prostate. There are no publications linking this gene to kidney function. |
| | **GRAIL** | *SKIL* p=0.02 | | |
| | **DEPICT** | *SKIL* FDR<0.05 | | |
| rs163160 (*KCNQ1*) | **eSNP** | NA | *KCNQ1* work already completed | *KCNQ1* encodes a voltage-gated potassium channel required for cardiac repolarization. RNA is ubiquitously expressed but the protein product is mostly expressed in glandular cells. In addition to be recognized as a gene conferring risk of T2D in Caucasians and more recently in African Americans,[94] it is also reported as a gene conferring susceptibility to diabetic nephropathy in Asians[95] and CKD in African Americans.[96] *TRPM5* encodes the transient receptor potential cation channel, subfamily M, member 5 gene, a member of the transient receptor potential (TRP) protein family with structural features typical of ion channels (non-selctive cations except Ca2+) and mediates a transient membrane depolarization in the presence of low concentrations of intracellular calcium. mRNA is found mainly in the prostate, testis, ovary, colon and leukocytes but the protein is expressed in the majority of human tissues. There are no publications linking this gene or its protein to kidney function. The tumor suppressing subtransferable candidate 4 (*TSSC4*) gene is located in the p15.5 region of the chromosome 11, a region involved in Wilm's tumor and a known important tumor-supressor gene region. TSSC4 RNA is widely expressed in human tissues while protein is strongly expressed in renal tubules and moderately in digestive system as well as male and female reproductive systems. |
| | **GRAIL** | NO | | |
| | **DEPICT** | *IGF2* (FDR<0.05 ) but very far away from lead SNP | | |

*Cited web resources: Entrez Gene: http://www.ncbi.nlm.nih.gov/gene; GenCards: www.genecards.org; OMIM: http://www.ncbi.nlm.nih.gov/omim; ProteinAtlas: www.proteinatlas.org; RefSeq: http://www.ncbi.nlm.nih.gov/refseq/; UCSC: www.genome.ucsc.edu.

**Supplementary Table 13**. DEPICT tissue and cell-type enrichment.*

| MeSH ID | Name | MeSH# first level term | MeSH second level term | P-value | FDR | Genes at associated loci§ |
|---|---|---|---|---|---|---|
| A05.810 | Urinary Tract | Urogenital System | Urinary Tract | 0.000226 | <0.025 | *NAT8, SLC17A3, SLC22A2, SLC17A1, LRP2, UMOD, SLC7A9, SLC6A13, SLC34A1, ENSG00000204872, PCK1, SLC47A1, WDR72* |
| A05.810.453 | Kidney | Urogenital System | Urinary Tract | 0.000292 | <0.025 | *NAT8, SLC17A3, SLC22A2, SLC17A1, LRP2, UMOD, SLC7A9, SLC6A13, SLC34A1, ENSG00000204872, PCK1, SLC47A1, WDR72* |
| A03.620 | Liver | Digestive System | Liver | 0.000663 | <0.025 | *ITIH1, LPA, SLC17A2, SLC22A1, ITIH3, KNG1, LEAP2, GCKR, SLC22A7, CPS1, A1CF* |
| A11.436.348 | Hepatocytes | Cells | Epithelial Cells | 0.001338 | <0.025 | *ITIH3, A1CF, LEAP2, SLC17A2, GCKR, AGMAT, ITIH1, SCGN, LCAT, SLC22A3, SLC7A9, SLC22A1* |
| A06.407.071.140 | Adrenal Cortex | Endocrine System | Endocrine Glands | 0.001574 | <0.025 | *ENSG00000256731, SLC47A1, FNDC4, KCNQ1, RERG, CASP9* |
| A06.407.071 | Adrenal Glands | Endocrine System | Endocrine Glands | 0.002988 | 0.025 | *SLC47A1, FNDC4, ENSG00000256731, KCNQ1, RERG, MAMSTR, CASP9* |

*DEPICT was used to assess whether genes at associated loci were highly expressed in any of 209 tissue and cell type annotations. In total we found 6 significantly enriched tissues (FDR < 0.05). Only significant tissues are shown in the table.

# MeSH: Medical Subject Headings.

§ Lists of genes that are within an associated region and highly expressed in the given tissue or cell type.

**Supplementary Table 14**. DEPICT pathway analysis**.** Gene sets with P-value < 1e–05 are shown.

| Reconstituted gene set ID | Reconstituted gene set name | Part of meta gene set | P-value | FDR | Reconstituted gene set genes at associated loci |
|---|---|---|---|---|---|
| ENSG00000186350 | RXRA protein complex | NCOA1 protein complex | 5.94E-08 | <0.002 | *NCOA6, SKIL, TRIB1, MED1, CDK12, EDC4, RELA, ARNT, ERBB2, PGAP3, NFATC1, PTPN12, NFKB1, A1CF, NRBP1, TPRKB, AFF4, NRIP1, NFATC3, INO80* |
| MP:0011423 | Kidney Cortex Atrophy | Dilated Renal Tubules | 3.40E-07 | <0.002 | *SLC7A9, SLC22A2, SLC34A1, VEGFA, NAT8, UMOD, DPEP1, AGMAT, PCK1, LRP2, PTPRO, IGF2, ENSG00000204872, ADAMTS5, DAB2, BMP4, SLC12A4, CA12, SLC6A13, TRIB1* |
| ENSG00000125124 | BBS2 protein complex | BBS4 protein complex | 4.76E-07 | <0.002 | *KNG1, UMOD, CPS1, ITIH3, ESRP2, RASIP1, PCK1, SLC7A9, AGMAT, SLC22A1, NAT8, LRP2, NUTF2, DACH1, ITIH4, EDC4, SLC22A2, ENSG00000204872, PSMD12, SGMS1* |
| ENSG00000124151 | NCOA3 protein complex | NCOA1 protein complex | 7.21E-07 | <0.002 | *TRIB1, MED1, NCOA6, FBXL20, ETV5, CDK12, VEGFA, GCKR, GLI2, RAI1, PSKH1, GTF3C2, MOV10, PIK3R1, PHLDA1, PGAP3, ITIH3, NFATC1, SETBP1, RMND5A* |
| MP:0003918 | Decreased Kidney Weight | Dilated Renal Tubules | 8.75E-07 | 0.002 | *RAPSN, IGF2-AS, ACVR2A, NFATC3, PCK1, NAT8, SLC7A9, SLC6A13, IGF2, SLC34A1, PTPRO, ADAMTS5, PAPPA, IGF2R, UMOD, GSS, LCAT, TCEA3, SVEP1, AGMAT* |
| GO:0015145 | Monosaccharide Transmembrane Transporter Activity | Monosaccharide Trans-membrane Transporter Activity | 1.21E-06 | 0.002 | *SLC7A9, ENSG00000204872, SLC34A1, AGMAT, LEAP2, NAT8, SLC22A2, TSPAN9, TRIM58, SLC2A9, DPEP1, C12orf68, ENSG00000230288, VEGFA, SLC28A2, DAB2, UMOD, SLC6A13, XYLB, OR2W3* |
| GO:0008514 | Organic Anion Transmembrane Transporter Activity | Organic Cationanionzwitterion Transport | 2.08E-06 | 0.006 | *SLC34A1, SLC22A2, NAT8, SLC6A13, KNG1, SLC22A7, UMOD, SLC22A1, ITIH1, SLC7A9, AGMAT, WDR72, ENSG00000204872, INHBC, SLC47A1, A1CF, LRP2, XYLB, PCK1, DPEP1* |
| MP:0000521 | Abnormal Kidney Cortex Morphology | Dilated Renal Tubules | 2.60E-06 | 0.005 | *UMOD, SLC7A9, SLC22A2, SLC34A1, AGMAT, VEGFA, NAT8, CA12, IGF2-AS, STC1, KNG1, GLI2, RASIP1, LRP2, DPEP1, EYA4, DACH1, SETBP1, PCK1, TSPAN9* |
| GO:2000117 | Negative Regulation Of Cysteine-Type Endopeptidase Activity | Negative Regulation Of Cysteine-Type Endopeptidase Activity | 3.26E-06 | 0.004 | *OR2W3, UMOD, SLC34A1, NRIP1, RMND5A, PSMA5, PRELID1, PTPN12, ENSG00000187446, SNX17, SLC7A6, ENSG00000232656, PSKH1, IZUMO1, SLC22A2, TRIB1, IDI1, NFE2L2, DCDC5, LRP2* |

**Supplementary Table 14** (continued).

| Reconstituted gene set ID | Reconstituted gene set name | Part of meta gene set | P-value | FDR | Reconstituted gene set genes at associated loci |
|---|---|---|---|---|---|
| MP:0001698 | Decreased Embryo Size | Complete Embryonic Lethality During Organogenesis | 4.30E-06 | 0.006 | *PTPN12, HNRNPR, NCOA6, HSPA4, IGF2, AFF4, IGF2R, ACVR2B, NSD1, VEGFA, MED1, CELF1, NRF1, BMP4, SETDB1, LAMA5, JARID2, RIF1, RMND5A, INO80* |
| MP:0011108 | Partial Embryonic Lethality During Organogenesis | Complete Embryonic Lethality During Organogenesis | 4.61E-06 | 0.005 | *IGF2, LAMA5, VEGFA, BMP4, TRIB1, RARB, PHLDA1, R3HDM2, RHOC, TSPAN9, JARID2, ACVR2B, AFF4, NSD1, PTPN12, SIPA1L3, RASIP1, A1CF, GLI2, GRB10* |
| MP:0001711 | Abnormal Placenta Morphology | Abnormal Placenta Labyrinth Morphology | 4.80E-06 | 0.005 | *VEGFA, ITIH1, GRHL2, TRIB1, KNG1, IGF2, SPATA5L1, NSD1, ITIH3, ESRP2, INO80, RHOC, LEAP2, LAMA5, CELF1, ARNT, ITCH, ERBB2, NCOA6, PAPPA* |
| GO:0005355 | Glucose Transmembrane Transporter Activity | Monosaccharide Transmembrane Transporter Activity | 5.07E-06 | 0.005 | *SLC7A9, ENSG00000204872, SLC34A1, AGMAT, SLC2A9, DPEP1, NAT8, SLC22A2, C12orf68, LEAP2, TRIM58, ENSG00000230288, VEGFA, SLC28A2, TSPAN9, GGT7, UMOD, SLC22A7, TFDP2, SLC6A13* |
| GO:0001655 | Urogenital System Development | Kidney Development | 5.43E-06 | 0.006 | *UMOD, EYA4, DACH1, SLC34A1, SLC22A2, RARB, DPEP1, IGF2-AS, ADAMTS5, IGF2, SETBP1, GRHL2, ERBB2, GLI2, LRP2, SHH, PAPPA, ACVR2B, BMP4, STC1* |
| GO:0015149 | Hexose Transmembrane Transporter Activity | Monosaccharide Transmembrane Transporter Activity | 6.45E-06 | 0.006 | *SLC7A9, ENSG00000204872, SLC34A1, AGMAT, SLC2A9, NAT8, SLC22A2, DPEP1, TSPAN9, LEAP2, C12orf68, TRIM58, ENSG00000230288, VEGFA, SLC28A2, GGT7, UMOD, PRELID1, SLC22A7, OR2W3* |
| MP:0002981 | Increased Liver Weight | Decreased Circulating Cholesterol Level | 7.33E-06 | 0.006 | *ITIH1, PCK1, KNG1, CPS1, LEAP2, SLC22A1, SLC22A7, ACSS2, SLC7A9, ITIH3, GCKR, IDI1, LPA, INHBC, FASN, A1CF, DPEP1, ITIH4, GSS, IGF2R* |
| GO:0072001 | Renal System Development | Kidney Development | 7.35E-06 | 0.005 | *UMOD, DPEP1, DACH1, SLC22A2, RARB, SLC34A1, ADAMTS5, EYA4, IGF2, IGF2-AS, SETBP1, BMP4, LRP2, NAT8, GLI2, SHH, CLDN11, ERBB2, LAMA5, CA12* |
| MP:0011346 | Renal Tubule Atrophy | Dilated Renal Tubules | 8.41E-06 | 0.005 | *UMOD, SLC34A1, SLC7A9, DPEP1, VEGFA, PTPRO, SLC47A1, AGMAT, SLC22A2, SLC22A7, KNG1, PCK1, MANBA, CPS1, ENSG00000204872, NAT8, WDR72, SLC2A9, LEAP2, SLC22A3* |
| MP:0005459 | Decreased Percent Body Fat | Abnormal Glucose Homeostasis | 8.78E-06 | 0.005 | *CTRL, CELA2B, TRIB1, PCK1, RAPSN, SORT1, ACSS2, SLC34A1, SLC7A9, ENSG00000187446, RSBN1L, FASN, STC1, THADA, LPA, PIK3R1, LMAN2, CASP9, IGF2R, PIGU* |

**Supplementary Table 15**. Zebrafish knock-down results**.***

| | MO | Dose | *Pax2a* | *Nephrin* | *Slc20a1a* |
|---|---|---|---|---|---|
| **Clutch 1** | **Control** | N/A | 0/33 (0%) | 0/36 (0%) | 0/51 (0%) |
| | ***Wnt7aa*** | 250 uM | 3/38 (8%)<br>p= 0.24 | 0/29 (0%) | 0/29 (0%) |
| | ***Nfkb1*** | 250 uM | 0/33 (0%) | 0/32 (0%) | 0/30 (0%) |
| | ***Ptpro*** | 250 uM | 0/22 (0%) | 0/27 (0%) | 0/14 (0%) |
| | ***A1cf*** | 250 uM | 0/31 (0%) | 0/36 (0%) | 0/23 (0%) |
| | ***Tspan9a+b*** | 125 uM each | 1/25 (4%)<br>p=0.43 | 0/22 (0%) | 1/19 (5%)<br>p=0.27 |
| | | | | | |
| **Clutch 2** | **Control** | N/A | 3/18 (17%) | 0/21 (0%) | 0/20 (0%) |
| | ***Kbtbd2*** | 250 uM | 0/20 (0%)<br>p=0.10 | 0/22 (0%) | 0/17 (0%) |
| | ***Uncx*** | 250 uM | 3/30 (10%)<br>p=0.66 | 1/26 (4%)<br>p=1.00 | 0/19 (0%) |
| | ***Dpep*** | 250 uM | 1/26 (4%)<br>p=0.29 | 1/23 (4%)<br>p=1.00 | 0/24 (0%) |
| | ***Sypl2a+b*** | 250 uM each | 7/35 (20%)<br>p=1.00 | 1/25 (4%)<br>p=1.00 | 0/29 (0%) |
| | | | | | |
| **Clutch 3** | **Control** | N/A | 0/37 (0%) | 0/55 (0%) | 0/41 (0%) |
| | ***Nfatc1*** | 250 uM | 2/26 (8%)<br>p=0.17 | 0/29 (0%) | 0/31 (0%) |
| | ***Skila+b*** | 62.5 uM each | 0/41 (0%) | 0/46 (0%) | 0/32 (0%) |

Zebrafish embryos were injected with morpholinos (MOs) targeting orthologous loci, and renal gene expression was assessed at 48 hours post-fertilization (hpf) by whole mount *in situ* hybridization. Renal markers examined include *pax2a* (global kidney), *nephrin* (podocyte), and *slc20a1a* (proximal tubule). Data are presented as the number of observed abnormalities per total number of embryos scored.

*P-values provided for non-0 results only.

**Supplementary Table 16**. Study information: discovery. Extensive study names are reported in the Acknowledgements section.

| Study[REF] | Study Design | N§ | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| 3C[97, 98] | Prospective population-based | 6440 | **Study exclusions or disease enrichment**. None. **Exclusions**. Of the 6440, those with genotypes and creatinine were 6431 and those with genotypes and cystatin C were 1243. | Modified kinetic Jaffe reaction. | Particle-enhanced immuno-nephelometric method (BNII, Dade-Behring/ Siemens) |
| Advance[99] | Randomised controlled trial | 11,140 | **Study exclusions or disease enrichment**. Multicenter trial done by 215 collaborating centres in 20 countries. All patients had T2D and were of Caucasian origin. Those with genotypes and creatinine were 2301. **Exclusions**. NA | Serum creatinine was measured in local laboratories at individual study sites. | NA |
| AGES[100] | Population based | 3664 | **Study exclusions or disease enrichment**. None. **Exclusions**. Sample exclusion criteria included sample failure, genotype mismatch with reference panel, and sex mismatch, resulting in clean genotype data on 3219 individuals. | Jaffé reaction. | NA |
| Amish[101, 102] | Population based "founder" cohort | 1264 | **Study exclusions or disease enrichment**. None. **Exclusions**. Age <20, severe chronic disease, call rate <95%, pHWE<10E-6. | Modified kinetic Jaffe reaction. | Particle-enhanced immunonephelometric method (BNII, Dade-Behring). |
| ARIC[103] | Prospective, population-based | 9713 | **Study exclusions or disease enrichment**. None. **Exclusions**. Of the 9713 genotyped individuals of European ancestry, we excluded 658 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives, or outlier based on measures of average DST or >8 SD away on any of the first 10 principal components. | Modified kinetic Jaffé reaction. | Particle enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring). |
| ASPS[104, 105] | Prospective study | 922 | **Study exclusions or disease enrichment**. Excluded were subjects with histrory of neuropsychiatric disease, previous stroke and/or TIA, and dementia. **Exclusions**. Of the 922 participants who underwent genotyping, we made the following exclusions: sample call rate <98% (74). This resulted in 848 genotyped individuals. | Modified kinetic Jaffé reaction. | NA |
| AUSTWIN[106] | Families, population-based | 9592 | **Study exclusions or disease enrichment**. NA. **Exclusions**. NA. | Jaffé method, Hitachi 917 analyser. | NA |
| BLSA[107] | Population based study | 1200 | **Study exclusions or disease enrichment**. None. **Exclusions**. Those of non-European descent or with missing phenotype information. | Modified kinetic Jaffé reaction. | NA |
| BMES[108-110] | Prospective cohort study | 2761 | **Study exclusions or disease enrichment**. None. **Exclusions**. Sample call rate <95% (n=9), outlying autosomal heterozygosity (n=28), sex discrepancies or ambiguous sample identification (n=69), cryptic relatedness (average IBD sharing proportion > 0.1875: n=121), non-European ancestry (n=13). This resulted in 2534 genotyped individuals. | Measured within 4 hours of collection using a Hitachi 747 Biochemistry analyser (Roche reagents, modified kinetic Jaffé). | NA |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design | N[§] | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| CHS[111, 112] | Prospective population-based | 3397 | **Study exclusions or disease enrichment**. A total of 1908 persons excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA.<br>**Exclusions**. The present report is based upon genotyping results from 3329 Caucasian participants, who were free of clinical cardiovascular disease at baseline, consented to genetic testing, and had DNA available for genotyping. Genotyping was successful in 3291 persons. | Colorimetric method (Ektachem 700, Eastman Kodak). | Particle-enhanced immunonephelometric assay [N Latex Cystatin C, Dade Behring (now Siemens), Deerfield, Ill, USA] with a nephelometer [BNII, Dade Behring (now Siemens)]. |
| CROATIA-KORCULA[113] | Cross-sectional, family-based | 888 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Subjects were excluded if they fulfilled any of the following criteria: genotypic call rate <97%; reported vs. genotypic sex mismatch; unexpectedly low genomic sharing with 1st degree relatives; excess of autosomal heterozygosity; outliers identified by IBS clustering analysis; pregnant women. | Jaffé rate method in plasma. | NA |
| CROATIA-SPLIT[114] | Population-based | 499 | **Study exclusions or disease enrichment**. Fasting urine and blood samples were collected from 1012 healthy volunteers aged 18+ from Split on the Dalmatian coast in Croatia in 2008/2011.<br>**Exclusions**. Missing creatinine levels | Jaffé protein compensated method in the serum. | NA |
| CROATIA-VIS[115, 116] | Cross-sectional, family-based | 768 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Subjects were excluded if they fulfilled any of the following criteria: genotypic call rate <97%, mismatch between reported and genotypic sex, unexpectedly low genomic sharing with first degree relatives, excess autosomal heterozygosity, or outliers identified by IBS clustering analysis. Pregnant women were excluded from the study. | Enzymatic photometric assay using an ADVIA1650 clinical chemistry analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany)[117] at the Institute for Clinical Chemistry and Laboratory Medicine, Regensburg University Medical Center, Germany. | NA |
| DESIR[118] | Population-based | 731 | **Study exclusions or disease enrichment**. Excluded 15 ethnicity outliers.<br>**Exclusions**. Individuals with genotype call rate <0.90, outlying heterozygosity, gender discrepancies, missing clinical data, cryptic relationships, non-European. | Kinetic colorimetry using Jaffé's Method. The assay utilized a Technicon DAX24 automated analyser from Bayer Diagnostics, Puteaux, France or a Specific or a Delta from Konelab, Evry, France. | NA |
| EGCUT 370K[119, 120]<br><br>EGCUT Omni[119, 120] | Population-based | 2700<br><br>9500 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Missing creatinine levels; genetic outliers; cryptic relatedness (one random member up to 2nd cousins was only included) | Modified Jaffé protein compensated method in the serum. | NA |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design | N[§] | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| ERF[121] | Population based family study | 2834 | **Study exclusions or disease enrichment**. None. **Exclusions**. NA. | Jaffé rate method using a Synchron LX20. | NA |
| FamHS[122] | Family based | 3838 | **Study exclusions or disease enrichment**. None. **Exclusions**. Age <18, call rate <98%, pHWE <10E-6, sex mismatch, non-European ancestry. | Thin film adaptation of the amidohydrolase enzymatic method using the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc. Rochester NY 14650). | Immune particle-enhanced turbidimetric (PET) kit (DAKO A/S, Produktionsvej 42, DK-2600 Glostrup, Denmark. Code no. K0071) |
| FHS[123-125] | Prospective family-based | 9300 | **Study exclusions or disease enrichment**. None. **Exclusions**. Of the 9,274 participants who underwent genotyping, we made the following exclusions: sample call rate <97% (n=666), genotype heterozygosity > 5 SDs, and ambiguous family data (n=127). This resulted in 8481 genotyped individuals. | Modified kinetic Jaffé reaction. | Particle-enhanced immunonephelometric method, Cystatin C was measured (BNII, Dade-Behring). |
| GENOA[126-128] | Family-based | 1553 | **Study exclusions or disease enrichment**. 5 Non-white, 1 Missing Exam. **Exclusions**. For the Affymetrix 6.0 data, we excluded 25 subjects who failed pre-processing, 123 with Contrast QC<0.4, 2 for inconsistent relatedness, 11 identical twins. We re-ran the samples that failed pre-processing or the Contrast QC filter on the Affymetrix 6.0 data along with 50 that had passed. Of these samples, 19 failed genotyping completely, 9 had call rate <0.95, 2 had inconsistent relatedness, and 2 were identical twins. Of the 1509 remaining samples, 346 had no serum creatinine information. Our final data had 1163 samples with genotype and phenotype data. | Compensated rate Jaffé reaction. | NA |
| HABC | prospective cohort study | 1663 | **Study exclusions or disease enrichment**. None. **Exclusions**. Sample failure, genotypic sex mismatch, and first-degree relative of an included individual based on genotype data. | Colorimetric technique on a Johnson & Johnson VITROS 950 Chemistry Analyzer (Johnson & Johnson, New Brunswick, N.J., USA) using the enzymatic method. | BNII nephelometer (Dade Behring Inc., Deerfield, Ill., USA) that utilized a particleenhanced immunonephelometric assay (N Latex Cystatin C). |
| HCS[129] | Population-based | 2204 | **Study exclusions or disease enrichment**. None. **Exclusions**. Individuals with genotype call rate <0.95, outlying heterozygosity, gender discrepancies, missing clinical data, cryptic relationships, non-European ancestry or missing creatinine measurement. | Siemens Dimension Vista 1500 Intelligent Lab System using a modified Jaffé assay in a NATA accredited lab. | NA |
| HPFS[130-134] | Nested case-control study of T2D | 2487 | **Study exclusions or disease enrichment**. All subjects had T2D. **Exclusions**. Of the 2487 subjects with genome-wide scans, 818 (all T2D cases) had creatinine measured. | Modified kinetic Jaffé reaction in plasma. | NA |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design# | N* | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| HYPERGENES HTN cases[135] | Cases from a nested case-control study of Hypertension | 2125 | **Study exclusions or disease enrichment**. We excluded 81 samples with call rate <0.95, 33 with genotypic sex mis-match, 39 duplicated, 94 related subjects, and 13 outliers. **Exclusions**. Of the 1865 subjects with GWA data after QC, 1591 had creatine measured | Kinetic Jaffé reaction. | NA |
| HYPERGENES HTN controls[135] | Controls from a nested case-control study of Hypertension | 1934 | **Study exclusions or disease enrichment**. We excluded 62 samples with call rate <0.95, 23 with genotypic sex mismatch, 25 duplicated, 62 related subjects, and 12 outliers. **Exclusions**. Of the 1750 subjects with GWA data after QC, 1662 had creatine measured | Kinetic Jaffé reaction. | NA |
| INCIPE[136] | Cross-sectional, population based | 940 | **Study exclusions or disease enrichment**. Excluded were individuals <40 year old. **Exclusions**. Pregnant women | Kinetic rates using the Jaffé method, recalibrated to standardized creatinine determinations obtained at the Cleveland Clinic Research Laboratory. | Immunonephelometric method that used monospecific antisera on an Immage 800 (Beckman Coulter). |
| INGI-CARLANTINO [137-139] | Isolated population | 679 | **Study exclusions or disease enrichment**. None. **Exclusions**. We obtained the levels of creatinine of 447 participants; excluded were those with call rate <97%. | Jaffè reaction. | NA |
| INGI-CILENTO[140-147] | Cross-sectional population-based study of isolated populations with pedigree information | 859 | **Study exclusions or disease enrichment**. None. **Exclusions**. 38 individuals aged <20 years | Modified kinetic Jaffé reaction. | NA |
| INGI-FVG[137-139] | Isolated population | 1376 | **Study exclusions or disease enrichment**. None. **Exclusions**. We obtained the levels of creatinine of 874 participants; excluded were those with call rate <97%. | Jaffé reaction. | NA |
| INGI-VAL BORBERA[148] | Family Population-based | 1665 | **Study exclusions or disease enrichment**. None. **Exclusions**. Of the 1665 participants who underwent genotyping, one was excluded because of a sample call rate <95%. | Jaffé reaction. | NA |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design | N[§] | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| JUPITER[149, 150] | Randomized, placebo-controlled trial | 8782 | **Study exclusions or disease enrichment**. Excluded were subjects with LDL-C ≥ 130 mg/dl or CRP < 2 mg/l.<br>**Exclusions**. None | Performed in JUPITER core central laboratories using the Roche Modular Analytics Chemistry System with Roche creatinine reagents (modified Jaffe reaction with rate blanking) (Roche Diagnostics, Township of Branchburg, New Jersey). | NA |
| KORA-F3[151, 152]<br><br>KORA-F4[151, 152] | Prospective population based | 1644<br><br>1814 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. None. | Modified kinetic Jaffe reaction. | Particle-enhanced immunonephelometric method (BNII, Dade-Behring). |
| MESA[153] | Community-based cohort study | 2520 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. NA. | Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY 14650). The laboratory analytical CV is 2.2%. All creatinine measurements for the MDRD Study were performed at Cleveland Clinic Labs using a CX3 assay. The Vitros analyzer used here was previously calibrated to a CX3 machine with the Cleveland Clinic lab and found the results were nearly identical. | BNII nephelometer (Dade Behring Inc., Deerfield, IL) that utilizes a particle enhanced immunonepholometric assay (N Latex Cystatin-C) 7 on fasting plasma specimens stored at -70°C. The assay is stable over 5 cycles of freeze / thaw. Among 61 healthy individuals with 3 cystatin-C measurements over a 6-month period, the intra-individual coefficient of variation was 7.7%. |
| MICROS[154-156] | Cross-sectional, population-based study on extended pedigrees | 1391 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Excluded were samples with overall SNP call rate <95%, showing excess of heterozygosity, or being classified as outliers by IBS clustering analysis. | Enzymatic photometric assay using an ADVIA1650 clinical chemistry analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany). | BN-ProSpec analyzer (Dade Behring, Marburg, Germany) at the Institute for Clinical Chemistry and Laboratory Medicine, Regensburg University Medical Center, Germany. |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design | N[§] | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| NESDA[157, 158] | Longitudinal cohort study | 1862 | **Study exclusions or disease enrichment**. Individuals were almost all cases with major depression or anxiety disorder (N=1705) and of Western-European ancestry.<br>**Exclusions**. Excluded were ethnic outliers, XO and XXY samples, and samples with a call rate <95%, high genome-wide homo- or heterozygosity, or excess of IBS. | Enzymatic assay from Roche Modular P unit (CREAplus; Roche Diagnostics, Ltd., Lewes, UK). Outliers (>4SD from mean) were excluded. | BNII nephelometer on plasma specimens (N Latex Cystatin C; Dade Behring Inc., Deerfield, IL). Excluded were values >4SD from the mean. |
| NHS[130, 132, 133, 159, 160] | Nested case-control study of T2D | 3286 | **Study exclusions or disease enrichment**. All individuals had T2D.<br>**Exclusions**. Of the 3286 subjects with GWA data, 784 had creatinine measured. | Modified kinetic Jaffé reaction in plasma. Creatinine values were not normalized to the Cleveland Clinic standard. | NA |
| NSPHS[161, 162] | cross-sectional, family-based | 565 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Subjects were excluded if they fulfilled any of the following criteria: genotypic call rate <97%, mismatch between reported and genotypic sex, unexpectedly low genomic sharing with first degree relatives, excess of autosomal heterozygosity, or outliers identified by IBS clustering analysis. | Enzymatic photometric assay in plasma using an ADVIA1650 clinical chemistry analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany). | NA |
| OGP-TALANA[163-165] | Isolated population | 1376 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. We obtained the levels of creatinine of 874 participants; exclusions were samples with call rate<97%. | Jaffé reaction. | NA |
| ORCADES[166] | cross-sectional, family-based | 704 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Subjects were excluded if they fulfilled any of the following criteria: genotypic call rate <97%, mismatch between reported and genotypic sex, unexpectedly low genomic sharing with first degree relatives, excess autosomal heterozygosity, or outliers identified by IBS clustering analysis. | Enzymatic photometric assay in plasma using an ADVIA1650 clinical chemistry analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany)[117] at the Institute for Clinical Chemistry and Laboratory Medicine, Regensburg University Medical Center, Germany. | NA |
| POPGEN[167] | Prospective population-based | 1163 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Samples with > 5% missing genotypes, showing excess genetic dissimilarity to the remaining subjects, or with evidence for a cryptic relatedness to other study participants were removed. These quality control measures left 1241 control samples for inclusion in the study. Of them, 1163 had serum creatinine available. All sex assignments could be verified by reference to the proportion of heterozygous SNPs on the X chromosome. | Enzymatic in vitro assay (CREAplus, Cobas®, Roche Diagnostics, Indianapolis, IN) | NA |
| PREVEND[168] | population based | 3634 | **Study exclusions or disease enrichment**. Subjects were aged 28 to 75 years and were enriched for microalbuminuria.<br>**Exclusions**. NA | NA | BNII nephelometer (Dade Behring Inc.). |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design | N[§] | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| PROSPER-PHASE[169-171] | randomized placebo controlled trial | 5763 | **Study exclusions or disease enrichment**. Subjects were included when they had had a vascular event or were at increased risk of vascular disease; age: 70-82.<br>**Exclusions**. After QC (sample rate <97.5%, genotype heterozygosity, ambigous family data), 5244 samples were available for analysis. | Measured at central laboratories, one in each of the three participating countries. | NA |
| RS-I[172-174] | Prospective population based study | 5974 | **Study exclusions or disease enrichment**. NA.<br>**Exclusions**. Excluded were samples with call rate < 97.5%, excess autosomal heterozygosity >0.336 (~FDR <0.1%), mismatch between called and phenotypic gender, or outliers identified by the IBS clustering analysis with >3 SDs from population mean or IBS probabilities >97%. | Modified kinetic Jaffé reaction. | NA |
| RS-II[172-174] | Prospective population based study | 1895 | **Study exclusions or disease enrichment**. NA.<br>**Exclusions**. Excluded were samples with call-rate <97.5%, excess of autosomal heterozygosity >0.336 (~FDR<0.1%), mismatch between called and phenotypic gender, and outliers identified by the IBS clustering analysis with >3 SDs from population mean or IBS probabilities >97%. | Modified kinetic Jaffé reaction. | NA |
| SAPALDIA | population based | 1444 | **Study exclusions or disease enrichment**. NA.<br>**Exclusions**. Excluded were subjects with cryptic relatedness and call rate <95%. | Jaffé reaction (Roche) and calibrated to the Roche enzymatic gold standard reference yielding slightly lower serum creatinine measurements than the Cleveland Clinic Jaffé reaction. | NA |
| SHIP[175, 176] | Prospective population-based | 4105 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Excluded were samples with call rate <92%, duplicate samples (by IBS estimation), individuals with reported/genotyped gender mismatch. | Jaffè method. (A blood sample was drawn from the cubital vein in the supine position - the participants were non-fasting due to the duration of the cumulative examinations, 4-6 hours in total). | Siemens N Latex Cystatin C assay, a particle-enhanced nephelometric immunoassay, on the BN ProSpec® System. |
| SHIP-TREND | Prospective population-based | 988 | **Study exclusions or disease enrichment**. Excluded were individuals with no genotype and those with known T2D.<br>**Exclusions**. Excluded were samples with call rate <94%, duplicate samples (by IBS estimation), individuals with reported/genotyped gender mismatch. | Jaffé method. | Dimension Vista® System, CYSC Flex® reagent cartridge, SIEMENS, Eschborn, Germany |
| SORBS[177-179] | Population-based | 1097 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Sample call rate<0.94; Ethnic outliers; duplicates; gender mismatch; IBS>0.2 | Kinetic enzymatic method. | NA |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 16** (continued).

| Study[REF] | Study Design | N[§] | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| WGHS[180] | Prospective population based | 21,940 | **Study exclusions or disease enrichment**. Excluded were individuals of non-European ancestry.<br>**Exclusions**. Samples with <98% successful SNP calls were excluded. Data had been collected on 21940 individuals had successful genotype information and verified European ancestry at the time of the analysis. | Rate-blanked method based on the Jaffé reaction using Roche Diagnostics reagents with reproducibility of 3.67% and 1.60% at concentrations of 1.17 and 6.40 mg/dL, respectively. | NA |
| YFS | Population based | 2023 | **Study exclusions or disease enrichment**. NA.<br>**Exclusions**. None. | Jaffé method (picric acid; Olympus Diagnostica GmbH) from frozen plasma samples in 2007. | NA |

Abbreviations: T2D = type 2 diabetes. §Total genotyped sample size.

**Supplementary Table 17**. Study information, replication. Extensive study names are reported in the Acknowledgements section.

| Study Name[REF] | Study Design | N§ | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| Bus Santé[181, 182] | Cross-sectional population-based | 5589 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Unsuccessful genotyping (N=106). Analyses were restricted to Caucasians, defined as self-reported citizenship corresponding to South / North America, Europe, and Australia regions (N=4671). Creatinine was available in 4408 participants. | Modified kinetic Jaffé reaction (Abbott Architect). | NA |
| EGCUT replic[120] | Population-based | 8576 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. Sample call rate <95% (N=279), genotype heterozygosity >5 SDs and ambiguous family data (N=264), gender mismatch (N=241). | Modified kinetic Jaffé reaction. | Immune turbidimetric method. |
| ESTHER[183-185] | Prospective cohort study | 3490 | **Study exclusions or disease enrichment**. Inclusion criteria: age ≥50 and good knowledge of German language.<br>**Exclusions**. Samples with insufficient amount of DNA were not genotyped. | Modified kinetic Jaffé reaction. | NA |
| GENDIAN[186, 187] | Cohort study of T2D complications | 1026 | **Study exclusions or disease enrichment**. After exclusion of N=53 subjects due to subject QC, excluded were patients with ESRD (N=438) or advanced, histologically proven diabetic nephropathy (N=84) or missing phenotype (N=1).<br>**Exclusions**: call-rate<95% (N=22); relatedness and duplicates (N=11); gender mismatch (N=16); ethnicity check (N=4). | Enzymatic assay. | Dade Behring assay (BNII) |
| GHS-I[188, 189]<br>GHS-II[188, 189] | Population-based | 3422<br>1438 | **Study exclusions or disease enrichment**. Excluded if age <35 and >74.<br>**Exclusions**: N=426 based on a call-rate <97%, a rate of heterorzygosity of 3 SDs away from the mean, disagreement between reported and genotypic sex, estimated IBD >0.25, IBS based principal components. This resulted in 2996 genotyped individuals. | Modified kinetic Jaffé reaction (Abbott). | NA |
| GSK[190-192] | Case-control study | 1776 | **Study exclusions or disease enrichment**. Cases were patients with unipolar recurrent depression; exclusion criteria: presence of manic or hypomanic episodes, mood incongruent psychotic symptoms, lifetime diagnosis of drug abuse and depressive symptoms secondary to alcohol or substance abuse or dependence or to a medical illness or medication. Controls: exclusion criteria: anxiety and affective disorders.<br>**Exclusions**: call-rate<98% (N=2). | Standard clinical chemistry assays from Roche Hitachi. | NA |
| HRS | Population-based Longitudinal | 12,507 | **Study exclusions or disease enrichment**. Non-European participants were excluded.<br>**Exclusions**. Sample call-rate<98%, gender discrepancy, unexpected duplicates and/or relatives with KC>1/32, missing cystatin C data. | NA | See note (1) |
| KORAF3 non-GWAS[151, 152]<br>KORAF4 non-GWAS[151, 152] | Prospective Population based | 1498<br>1202 | **Study exclusions or disease enrichment**. None.<br>**Exclusions**. None. | Modified kinetic Jaffé reaction. | Particle-enhanced immunonephelometric method (BNII, Dade-Behring). |

§ Total genotyped sample size.

(1) Measured from dried blood spots (DBS) obtained during a face-to-face interview with the respondent at the same time as saliva collection. Blood was taken by pricking the participant's finger with a sterile lancet after cleansing the finger with an alcohol swab. Droplets of blood were extracted from the finger and directly placed on specially treated filter paper. Cystatin C for was assayed at the University of Vermont in 2006 and 2008. Serum equivalent values were calculated using a formula derived from a validation study done in conjunction with the USC/UCLA Center on Biodemography and Population Health.

**Supplementary Table 17** (continued).

| Study Name[REF] | Study Design | N§ | Study characteristics | Creatinine Measurement | Cystatin measurement |
|---|---|---|---|---|---|
| IPM[193] | Hospital-based | 1747 | **Study exclusions or disease enrichment**. None. **Exclusions**. None. | Colorimetric method in (CPT82565) performed by the New York State / CLIA Clinical Chemistry Laboratory at Mount Sinai Medical Center. | NA |
| LURIC[194] | Case control | 3061 | **Study exclusions or disease enrichment**. Inclusion criteria: Caucasian, availability of coronary angiogram, stable condition except acute coronary syndrome. Exclusion criteria: any chronic disease other than cardiovascular, any acute illnesss other than ACS, any malignancy in the previous five years. **Exclusions**. Sample call-rate<95%, ambiguous sex, duplicates, relatedness. This resulted in 3061 genotyped individuals. | Jaffé method (CREA/Hitachi 717). | N LATEX Cystatin C/ Behring nephelometer II. |
| OGP[163-165] | Population-based study with pedigree information | 9554 | **Study exclusions or disease enrichment**. None. **Exclusions**. NA. | Modified kinetic Jaffé reaction or enzymatic reaction. | NA |
| SAPHIR[195, 196] | Healthy working population | 1726 | **Study exclusions or disease enrichment**. None. **Exclusions**. None. | Modified kinetic Jaffé reaction (CREA®, Roche Diagnostics GmbH, Mannheim, Germany). | NA |
| SKIPOGH[197] | cross-sectional family-based population-based | 941 | **Study exclusions or disease enrichment**. None. **Exclusions**. Excluded were 71 participants with call-rate <90%, resulting in 870 genotyped individuals. | IDMS-traceable Jaffé kinetic compensated method. | NA |
| Vanderbilt Omni1<br><br>Vanderbilt Omni5 | Practice-based cohort | 5184<br><br>2005 | **Study exclusions or disease enrichment**. Samples chosen based on being a case or control for one of 31 pharmacogenetic analyses. **Exclusions**. Excluded individuals of non-white ancestry in the electronic medical record. Also excluded any lab measurements of individuals after initiation of dialysis or a kidney transplant. The median outpatient creatinine value was chosen. | Jaffé reaction. | NA |
| Vanderbilt 660W | Practice-based cohort | 3021 | **Study exclusions or disease enrichment**. Samples chosen for normal cardiac conduction, meaning that at some point in time they had a normal electrocardiogram without the presence of heart disease, arrhythmias, or electro-cardiographically-active medications. **Exclusions**. Children (age<18) and individuals of non-white ancestry in the electronic medical record. Also excluded any lab measurements from individuals after initiation of dialysis or a kidney transplant. The median outpatient creatinine value was chosen. At some point in their electronic medical record, the patients were absent of heart disease, but could later develop it. | Jaffé reaction. | NA |

§ Total genotyped sample size.

**Supplementary Table 18.** Genotyping information, discovery studies.

| Study name | Array type | Genotype calling | QC filters genotyped SNPs used for imputation‡ | No. of SNPs used for imputation | Imputation software | Imputation Backbone (NCBI build) | Filtering of imputed genotypes† | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| 3C | Illumina Human610-Quad | Illumina BeadStudio | call rate < 98%, pHWE<10e-6, MAF<1% | 492,897 | MACH | 1000 Genomes - CEU - Dec 2010 (build 37) | none | R, ProbABEL |
| Advance | Affymetrix 5.0 Affymetrix 6.0 | Affymetrix | Affymetrix 5.0: call rate < 96% (<99% if MAF < 5%); Affymetrix 6.0: call rate < 97% (<99% if MAF<5%) | 876,688 | IMPUTE 2 v2.1.2 | 1000 Genomes - CEU Pilot - Jun 2010 plus HapMap3 rel. 2 (all available haplotypes) – Feb 2009 (build 36) | imputation info<0.5 | SNPTEST |
| AGES | Illumina Hu370CNV | Illumina | pHWE<1e-6, call rate<97%, mishap p<1e-9, MAF<1%, SNPs not in Hapmap or with strand issues when merging with Hapmap | 329,804 | MACH v1.0.16 | HapMap rel. 22 (build 36) | none | R, ProbABEL, Linear and Logistic Regression |
| Amish | Affymetrix 500K | BRLMM | MAF<1%, non-HapMap, call rate < 95%, pHWE<10e-6 | 338,598 | MACH v1.0.15 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | Measured genotype accounting for polygenic component |
| ARIC | Affy 6.0 | Birdseed | call rate <95%, MAF<1%, pHWE <10e-5 | 669,450 | MACH v1.0.16 | HapMap rel. 22 (build 36) | none | R, ProbABEL, PLINK |
| ASPS | Illumina Human610-Quad BeadChip | Illumina | pHWE<1e-6, call rate < 98%, mishap p<1e-9, MAF<1%, Mendelian errors>100, SNPs not in Hapmap or with strand issues when merging with Hapmap | 550,635 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R, linear and logistic fixed effects model |
| AUSTWIN | Illumina370, iLLumina610 | BeadStudio-gencall v3.0 | call rate < 95%, pHWE<1e-6 | 271,069 | MACH v1.0.15 | HapMap rel. 22 - phased CEU haplotypes (build 36) | Rsq<0.3 | Stata, SPSS |
| BLSA | Illumina Infinium HumanHap 550K | BeadStudio | call rate <99%, MAF <1%, pHWE<10e-4 | 501,764 | MACH v1.0.15 | HapMap rel. 21 - phased CEU haplotypes (build 35) | MAF<0.01, r2hat < 0.3 | SAS, MERLIN, R |

**Supplementary Table 18** (continued).

| Study name | Array type | Genotype calling | QC filters genotyped SNPs used for imputation‡ | No. of SNPs used for imputation | Imputation software | Imputation Backbone (NCBI build) | Filtering of imputed genotypes† | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| BMES | Illumina 670K-Quad | CHIAMO | call rate <95%, pHWE<10e-6, MAF<1%, genotype discrepancies in > 2.5% of 1356 samples independently genotyped for the Illumina 610K array | 501,910 | MACH v1.0.16 | HapMap rel. 22 - phased CEU haplotypes (build 36.1) | none | Plink, mach2dat, SAS |
| CHS | Illumina 370CNV | Illumina BeadStudio | call rate<97%, heterozygotes=0, pHWE<10e-5, SNP not in HapMap | 306,655 | BimBam v0.99 | HapMap CEU rel. 22 (build 36) | dosage variance < 0.01 | R, linear and logistic regression, robust SE estimates |
| CROATIA-KORCULA | Illumina Infinium HumanCNV370 v1 SNP bead microarrays | BeadStudio | MAF<1%, pHWE<1e-6, call rate < 98% | 317,896 | MACH v1.0.16 | HapMap rel. 22 (build 36) | none | R, GenABEL, ProbABEL; |
| CROATIA-SPLIT | Illumina HAP370CNV | Illumina | call rate <98%, pHWE<10e-10 | 330,997 | MACH v1.0.15 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | R (GenABEL, ProABEL) |
| CROATIA-VIS | Illumina HumanHap300 beadchip | BeadStudio | MAF≤1% , pHWE ≤1e-6 , call rate ≤ 98% | 305,068 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R, GenABEL, ProbABEL; |
| DESIR | Illumina Human CNV370-Duo Array and Illumina HAP300 array | Illumina Beadstation Genotyping Solution | call rate < 95% p HWE < 1e-4 | 291,609 | IMPUTE v0.3.2 (genotyped SNPs used where available) | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | SNPTEST v2.2.0 |
| EGCUT 370K | Illumina 370CNV; Illumina OmniExpress | GenCall GenomeStudio | call rate <95%, pHWE<10e-6, MAF<1% | 320784; 622800 | IMPUTE v1.0 | HapMap 2 CEU rel. 22 | none | PLINK |
| EGCUT Omni | Illumina 370CNV; Illumina OmniExpress | GenCall GenomeStudio | call rate <95%, pHWE<10e-6, MAF<1% | 320784; 622800 | IMPUTE v1.0 | HapMap 2 CEU rel. 22 | none | PLINK |
| ERF | Illumina 6K/318K/380K, Affy 250K | BeadStudio (Affymetrix) | pHWE<1e-6, call rate<98%, MAF<1%, gender mismatch, excess heterozygosity | 487,573 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R, GenABEL, ProbABEL (linear mixed effect models) |
| FamHS | Illumina 550K, Illumina 610K, and Illumina 1M | BeadStudio-GenCall v3.0 | call rate <98%, pHWE<10e-6, MAF<1% | 499,979 | MACH v1.0.16 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | R (quantitative traits), SAS (qualitative trait) |

**Supplementary Table 18** (continued).

| Study name | Array type | Genotype calling | QC filters genotyped SNPs used for imputation‡ | No. of SNPs used for imputation | Imputation software | Imputation Backbone (NCBI build) | Filtering of imputed genotypes† | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| FHS | Affymetrix 500K Affymetrix 50K Supplementary | Affymetrix | call rate <95%, pHWE<10e-6 | 503,526 | MACH v1.0.15 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | R |
| GENOA | Affymetrix 6.0 (primary), Illumina 610-Quad, Illumina 660-Quad, Illumina 1M-Duo | Birdseed (Affymetrix data), Genome Studio (Illumina data) | call rate < 95%, pHWE < 0.001, MAF<1% | 1,233,495 (because of the different platforms, some SNPs may have had many missings) | MACH v1.0.16 | HapMap CEU rel. 22 (build 36) | none | R, multic and GEE |
| HABC | Illumina 1M | BeadStudio v3.3.7 | MAF<1%, call rate < 97%, pHWE<1e-6 | 914,263 | MACH v1.0.16 | HapMap CEU rel. 22 (build 36) | None | R, linear regression and logistic regression |
| HCS | Illumina 610K-Quad | Illumina | call rate <95%, pHWE<10e-6, MAF<1% | 513,977 | MACH v1.0.16 | HapMap rel. 24 - phased CEU haplotypes (build 36.1) | MAF<0.01, Rsq<0.3 | plink, SAS |
| HPFS | Affymetrix Genome-Wide Human 6.0 array | Birdseed | call rate <97%, pHWE<10e-4, MAF <0.02, more than 1 discordance over 29 replicates, significant plate associations | 607,569 (autosomal) | MACH v1.0.15 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | ProbABEL (R), SAS 9.0, PLINK |
| HYPERGENES HTN cases | Illumina 1M Duo | Illumina | call rate <99%, pHWE<10e-8 | 882,935 | MACH v1.0 | HapMap rel. 22 - phased CEU haplotypes (build 36) | Rsq<0.3 | PLINK, R |
| HYPERGENES HTN ctrls | Illumina 1M Duo | Illumina | call rate <99%, pHWE<10e-8 | 882,935 | MACH v1.0 | HapMap rel. 22 - phased CEU haplotypes (build 36) | Rsq<0.3 | PLINK, R |
| INCIPE | Illumina | Illumina | call rate <95%, pHWE<10e-6 | 635,646 | IMPUTE 2 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | R |
| INGI-CARLANTINO | Illumina 370K | BeadStudio | MAF<5%, call rate < 90%, pHWE < 0.05 | 374,498 | MACH | HapMap rel. 22 (build 36) | Rsq<0.3 and <5 copies of the rare allele. | R, GenABEL, mmscore |
| INGI-CILENTO | 370 K Illumina | Illumina | call rate < 95%, SNPs not in Hapmap | 285,674 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R, linear model, GenABEL, ProbABEL (mmscore) |
| INGI-FVG | Illumina 370K | BeadStudio | MAF<5%, call rate < 90%, pHWE < 0.05 | 374,498 | MACH | HapMap rel. 22 (build 36) | Rsq<0.3 and <5 copies of the rare allele. | R, GenABEL, mmscore |

**Supplementary Table 18** (continued).

| Study name | Array type | Genotype calling | QC filters genotyped SNPs used for imputation‡ | No. of SNPs used for imputation | Imputation software | Imputation Backbone (NCBI build) | Filtering of imputed genotypes† | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| INGI-VAL BORBERA | Illumina SNP array 370K - HumanCNV370 -Quadv3 | BeadStudio | pHWE<1e-4, call rate < 90%, MAF<1% | 324,319 | MACH | HapMap rel. 22 (build 36) | none | R |
| JUPITER | Omni 1M Quad | Illumina | sample call rate <98%, call rate < 90%, pHWE<1e-6 | 740,416 | MACH v1.0 | 1000 Genomes - CEU - Pilot - Jun 2010 | none | R, probABEL |
| KORA-F3 | Affymetrix 500K | BRLMM | per-chip call rate <93%, MAF <5%,discrepancy for one of the 50 SNPs common on both chips, gender mismatch | 380,407 | MACH | HapMap rel. 22 (build 35) | none | MACH2QTL, PROBABEL, R, VISUAL BASIC |
| KORA-F4 | Affymetrix 6.0 | BRLMM | per-chip call rate <93%, per SNP call rate <93%, MAF<1%, gender mismatch | 629,893 | MACH | HapMap rel. 22 (build 36) | none | MACH2QTL, PROBABEL, R, VISUAL BASIC |
| MESA | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed v2 | call rate < 95%, MAF≤1% | 897,979 | IMPUTE v2.1.0 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | PLINK |
| MICROS | Illumina Infinium HumanHap300 v2 SNP bead microarrays | BeadStudio | call rate <98%, MAF<1%, pHWE<10e-6 | 292,917 | MACH v1.0.16 | HapMap rel. 22 (build 36) | none | R, GenABEL, ProbABEL; |
| NESDA | Perlegen 600K | Perlegen | call rate <95%, MAF<1%, >5% genotype mismatches, >5% Mendelian errors, unknown SNP location | 435,291 | IMPUTE v0.4.2 | HapMap rel. 24 - phased CEU haplotypes (build 36) | none | SNPTEST v2.2.0, R |
| NHS | Affymetrix Genome-Wide Human 6.0 array | Birdseed | call rate <97%, pHWE<10e-4, MAF <2%, >1 discordance/12 replicates, significant plate associations | 606,626 (autosomal) | MACH v1.0.15 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | R, ProbABEL, SAS 9.0, PLINK |
| NSPHS | Illumina 300K | BeadStudio | MAF≤1%, pHWE≤1e-5 , call rate ≤ 97% | 318,049 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R, GenABEL, ProbABEL |
| OGP-TALANA | Affymetrix500k | Affymetrix | call rate <95%, pHWE<10e-6 | 329,122 | MACH v1.0.16 | HapMap rel. 22 - phased CEU haplotypes (build 36) | Rsq<0.3 | R, GenABEL, ProbABEL (mmscore) |
| ORCADES | Illumina 300K | BeadStudio | MAF≤1%, pHWE ≤ 1e-6, call-rate ≤ 98% | 306,207 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R, GenABEL, ProbABEL |

**Supplementary Table 18** (continued).

| Study name | Array type | Genotype calling | QC filters genotyped SNPs used for imputation‡ | No. of SNPs used for imputation | Imputation software | Imputation Backbone (NCBI build) | Filtering of imputed genotypes† | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| POPGEN | Affymetrix 6.0 | Birdseed v2 | sample call rate < 0.90, call rate < 0.95, pHWE<1e-4, MAF<1% | 709,003 | MACH v1.0.16 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | PLINK, R |
| PREVEND | Illumina CytoSNP12 v2 | GenomeStudio | call rate < 95%, pHWE<1e-5 | 232,571 | | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | STATA |
| PROSPER-PHASE | Illumina 660K | Illumina | call rate < 97,5% | 557 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | R |
| RS-I | Version 3 Illumina Infinium II HumanHap550 | BeadStudio | pHWE<1e-5, call rate<90%, MAF<1%, Mendelian errors > 100, SNPs not in Hapmap or strandedness issues merging with Hapmap | 491,875 | MACH | HapMap rel. 22 (build 36) | none | ProbABEL |
| RS-II | Version 3 Illumina Infinium II HumanHap550 | BeadStudio | pHWE<1e-5, call rate<90%, MAF<1%, Mendelian errors>100, SNPs not in Hapmap or strandedness issues merging with Hapmap | 495,478 | MACH | HapMap rel. 22 (build 36) | none | ProbABEL |
| SAPALDIA | Illumina Human610-Quad BeadChip | Gencall | none | 567,589 | MACH v1.0.16 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | ProbABEL, STATA v11 |
| SHIP | Affymetrix 6.0 | Affymetrix Birdseed2 | none | 869,224 | IMPUTE v0.5.0 | HapMap rel. 22 (build 36) | none | SNPTEST v1.1.5, QUICKTEST v0.94, R, InforSense, InterSystems Caché, |
| SHIP-TREND | Illumina Human Omni 2.5 | Illumina | pHWE ≤ 1e-4, call rate ≤ 0.9, monomorphic SNPs | 1,782,967 | IMPUTE v2.1.2.3 | HapMap rel. 22 - phased CEU haplotypes (build 36) | duplicated rsID with different positions | QUICKTEST v0.95, R, InforSense, InterSystems Caché |

**Supplementary Table 18** (continued).

| Study name | Array type | Genotype calling | QC filters genotyped SNPs used for imputation‡ | No. of SNPs used for imputation | Imputation software | Imputation Backbone (NCBI build) | Filtering of imputed genotypes† | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| SORBS | 500K Affymetrix GeneChip (250K Sty and 250K Nsp arrays, Affymetrix, Inc) and Affymetrix Genome-Wide Human SNP Array 6.0 | Microarray Core Facility of the Interdisciplinary Centre for Clinical Research, University of Leipzig, Germany and ATLAS Biolabs GmbH, Berlin, Germany | MAF<1%, pHWE<1e-4, call rate < 95%, | 378,513 | IMPUTE | HapMap CEU rel. 21 (build 35) | proper_info ≤ 0.4 | ProbAbel with robust variance option to account for remaining relatedness |
| WGHS | Illumina HumanHap300 Duo "plus" | BeadStudio v3.1 | pHWE<1e-6, call rate < 98%, MAF<1% | 331,993 | MACH v1.0.15 | HapMap rel. 22 (build 36) | none | PLINK, R, ProbAbel |
| YFS | Illumina 670k custom | Illuminus | call rate <95%, pHWE<10e-6 | 546,674 | IMPUTE 2.1.2 | 1000 Genomes - Jun 2011 phased haplotypes | none | SAS |

‡QC filters for genotyped SNPs used for imputation (SNPs satisfying the filter were excluded).

†Filtering of imputed genotypes (SNPs satisfying the filter were excluded).

**Supplementary Table 19**. Genotyping platform – *in silico* replication studies.

| Study Name | Array type | Genotype calling | QC filters for genotyped SNPs used for imputation | No of SNPs used for imputation | Imputation | Imputation Backbone (NCBI build) | Filtering of imputed genotypes | Data management and statistical analysis |
|---|---|---|---|---|---|---|---|---|
| EGCUT-replic | Illumina OmniExpress | Genome Studio (GenCall) | call rate<95%, pHWE<10e-6, MAF<1% | 616,063 | IMPUTE v2.2 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | Plink, SNPTEST 2, R |
| GENDIAN | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed (BRLMM) | N=126,259 SNPs (chr 1-chr22, chr X) were excluded from imputation by SNP quality control. | 776,075 | Mach 1.0.18.c MiniMac 2012-10-09 | GIANT ALL 1000 Genomes v3 ref panel GRCh build 37 | none | R |
| GSK cases/controls | Illumina 550 K | Illumina | call rate <98%, pHWE<10e-5 | 522,008 | IMPUTE v2 | CEU in HapMap3 and 1000 Genomes Pilot 1 | none | R, Plink |
| Gutenberg Health Study | Affymetrix 6.0 | Birdseed | call rate<95%, MAF<1%, pHWE<10e-4 | 662,405 | IMPUTE v2.1.0 | HapMap rel. 24 (build 36) | none | R |
| HRS | Illumina Omni2.5 Beadchip | Genome Studio v2011.2 | call rate <98%, pHWE<10e-4 | 551,936 | MACH v1.0.16 | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | SAS, R |
| IPM_EA_Affy | Affymetrix 6.0 | Birdseed | sample call rate <95%, SNP call rate <95%, pHWE<1e-4, MAF<1% | 711,270 | IMPUTE 2 | Phase I integrated variant set release (v3) (NCBI build 37) | none | SNPTEST 2, R |
| IPM_EA_Illu | Illumina Human OmniExpress Exome-8v1 | Genome Studio | sample call rate <99%, SNP call rate <95%, pHWE<5e-5, MAF<1% | 865,711 | IMPUTE 2 | Phase I integrated variant set release (v3) (NCBI build 37) | none | SNPTEST 2, R |
| LURIC | Affymetrix 6.0 | Birdseed v2 | call rate <98%, pHWE<10e-4 | 686,195 | MACH | HapMap rel. 22 - phased CEU haplotypes (build 36) | none | QUICKTEST |
| Vanderbilt Omni1 | Illumina HumanOmni1-Quad | BeadStudio | call-rate<98%, IBD (Z0<0.8), Mendel errors >0, Duplicate concordance <100% | 946,523 | IMPUTE v2.3.0 | 1000 Genomes Phase 1 integrated v3 | Genotype Likelihood <0.9 | Plink, R |
| Vanderbilt Omni5 | Illumina HumanOmni5-Quad | BeadStudio | call rate <98%, IBD (Z0<0.8), Mendel errors >0, Duplicate concordance <100% | 3,819,154 | IMPUTE v2.3.0 | 1000 Genomes Phase 1 integrated v3 | Genotype Likelihood <0.9 | Plink, R |
| Vanderbilt 660W | Illumina Human660W-Quad | BeadStudio | call rate <98%, IBD (Z0<0.8), Mendel errors >0, Duplicate concordance <100% | 530,014 | IMPUTE v2.3.0 | 1000 Genomes Phase 1 integrated v3 | Genotype Likelihood <0.9 | Plink, R |

**Supplementary Table 20**. Genotyping information: *de novo* replication studies.

| Study Name | Bus Santé | ESTHER | KORA F3 and F4 | OGP | SAPHIR | SKIPOGH |
|---|---|---|---|---|---|---|
| **Genotyping platform** | LGC Genomics SNP-line, using KASP™ Chemistry and 1536-well plates | LGC Genomics SNP-line, using KASP™ Chemistry | MALDITOF MS, Bruker Daltonik GmbH, Leipzig, Germany | LGC Genomics SNP-line, using KASP™ Chemistry | Sequenom platform | LGC Genomics SNP-line, using KASP™ Chemistry and 1536-well plates |
| **Amount of DNA used per SNP** (in ng) | DNA amplified, but typically 5 -7.5 ng of gDNA per genotype | 3.75 ng | 1 ng | 5 ng | 15 ng | 5 -7.5 ng of gDNA per genotype |
| **Genotyping method** | See note[1] | See note[1] | iPlex Gold | See note[1] | Mass ARRAY Analyzer 4 system | See note[1] |
| **No. of duplicates and concordance per SNP (provided per individual SNP)** | Not duplicated | LGC Genomics does not add duplicates. The data for each SNP represents one reaction per sample. | At least 15% duplicate genotyping per SNP. Concordance≥95%, median = 100% | LGC Genomics does not add duplicates. The data for each SNP represents one reaction per sample. | 70 duplicates; of 46 SNPs genotyped, 44 had a concordance of 100%, 2 had 1 discordant sample each | 29 samples genotyped in duplicate. SNP concordance varied from 86% to 100%. |
| **Number attempted / number genotyped samples per individual SNP** | The genotyping call rate (%) was typically between 0.95-0.97 | Call-rate range 0.98-1 | NA | Allele call rate 0.99 | 46 SNPs were genotyped: mean call-rate = 99.3% (min = 98.15%, max = 99.65%) | Median SNP call-rate = 97.2% (min =94.5%, max = 99.5%) |
| **Other QC laboratory-specific indices** | See note[2] | none indicated by the lab | NA | none indicated by the lab | automatic calculation of the HWE, comparision of the obtained genotypes with HapMap Data | See note[2] |

[1] Genotyped using KASPar (Kompetitive Alelle Specific PCR) v4.0 after whole genome amplification by primer extension preamplification (PEP) using thermostable DNA polymerases.

[2] All assays have been validated on an in-house DNA panel (44 random Caucasian DNA samples). All sample plates genotyped include at least two negative controls. ie. blank/water controls. All genotyping data is initially generated by an automated algorithm (genotype calling based upon recorded fluorescence values). All genotyping data is manually checked and verified by no less than two experienced scientists at LGC genomics.

**Supplementary Table 21**. Morpholino (MO) sequences.

| Target gene | Splice or ATG | MO sequence |
|---|---|---|
| *A1cf* | ATG | 5' CCCCACATTTTTGATTGGTTTCCAT 3' |
| *Dpep* | ATG | 5' AATCTTGACCCATTCCATCATCACC 3' |
| *Kbtbd2* | ATG | 5' TGTTCGTATCCCATGAGTTTTCAAC 3' |
| *Nfatc1* | Splice | 5' CGCATCTGTAAGGTACAATCACATT 3' |
| *Nfkb1* | ATG | 5' TCCTCGCCAGCCATGATTCCTTTGC 3' |
| *Ptpro* | ATG | 5' GATCGCACTCTTTGATTCTCGGCGT 3' |
| *Skila* | Splice | 5' TTGCCCTGCAAACACACATACACAC 3' |
| *Skilb* | Splice | 5' CCCGGATGACTGAAACAAGTCAAAA 3' |
| *Sypl2a* | Splice | 5' TTGAAATGTGGTTGTTTATACCTGA 3' |
| *Sypl2b* | Splice | 5' AGACTCTTTAATGAGGTTTACCTAA 3' |
| *Tspan9a* | Splice | 5' GTAGGAGTGGCAAAACTTACGCTCA 3' |
| *Tspan9b* | ATG | 5' GCACAGGCATCCACGAGCCATCTTC 3' |
| *Uncx* | Splice | 5' ATCCCCCGAATCTATGTAAGAAACA 3' |
| *Wnt7aa* | ATG | 5' TCCAGCGGCGCGTTTTCCTGCTCAT 3' |

## Supplementary Note.

Study specific acknowledgements and funding sources for participating studies, alphabetical order.

**3C**. *Three-City Study*. The work was made possible by the participation of the control subjects, the patients, and their families. We thank Dr. Anne Boland (CNG) for her technical help in preparing the DNA samples for analyses. This work was supported by the National Foundation for Alzheimer's disease and related disorders, the Institut Pasteur de Lille and the Centre National de Génotypage. The 3C Study was performed as part of a collaboration between the Institut National de la Santé et de la Recherche Médicale (Inserm), the Victor Segalen Bordeaux II University and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study was also funded by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Aquitaine and Bourgogne Regional Councils, Fondation de France and the joint French Ministry of Research/INSERM "Cohortes et collections de données biologiques" programme. Lille Génopôle received an unconditional grant from Eisai.

**Advance**. *Action in Diabetes and Vascular disease: preteraX and diamicroN mr Controlled Evaluation study*. The genetic epidemiological work was funded by Prognomix Inc. and by grants from Genome Quebec and Canadian Institutes for Health Research (CIHR). The clinical study was managed by the George Institute for International Health (Sydney, Australia) with grants received from Les Laboratoires Servier, France and from Medical Research Council of Australia. The genotyping was performed at the genomic platform of CRCHUM. The authors acknowledge the technical help of Carole Long and Mounsif Haloui and the bioinformatic analyses performed by Gilles Godefroid, François-Christophe Blanchet-Marois and François Harvey. The members of the genetic sub-study of ADVANCE, Stephen Harrap and Michel Marre are also acknowledged.

**AGES**. *Age, Gene/Environment Susceptibility-Reykjavik Study*. This study has been funded by NIH contract N01-AG-1-2100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

**Amish**. *Amish studies*. We thank our Amish research volunteers for their long-standing partnership in research, and the research staff at the Amish Research Clinic for their work. We are supported by grants and contracts from the NIH including R01 AG18728 (Amish Longevity Study), R01 HL088119 (Amish Calcification Study), U01 GM074518-04 (PAPI Study), U01 HL072515-06 (HAPI Study), U01 HL084756 and NIH K12RR023250 (University of Maryland MCRDP), the University of Maryland General Clinical Research Center, grant M01 RR 16500, the Baltimore Veterans Administration Medical Center Geriatrics Research and Education Clinical Center and the Paul Beeson Physician Faculty Scholars in Aging Program.

**ARIC**. *Atherosclerosis Risk in Communities study*. The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. This work as well as YL and AK were supported by the Emmy Noether Program of the German Research Foundation (KO 3598/2-1 to AK).

**ASPS**. *Austrian Stroke Prevention Study*. The research reported in this article was funded by the Austrian Science Fond (FWF) grant number P20545-P05 and P13180. The Medical University of Graz supports the databank of the ASPS. The authors thank the staff and the participants of the ASPS for their valuable contributions. We thank Birgit Reinhart for her long-term administrative commitment and Ing Johann Semmler for the technical assistance at creating the DNA-bank.

**AUSTWIN**. The *Australian Twin-Family Studies* were supported by NIH grants AA07535, AA07728, AA13320, AA13321, AA13326, AA14041, AA11998, AA17688, DA012854, DA019951; by grants from the Australian National Health and Medical Research Council (241944, 339462, 389927, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 552485, 552498); from the Australian Research Council (A7960034, A79906588, A79801419, DP0770096, DP0212016, DP0343921); and the FP-5 GenomEUtwin Project (QLG2-CT-2002-01254). Genotyping was partially supported by grant AA13320 to the late Richard Todd, PhD, MD. R.P.M., and G.W.M. are supported by the National Health and Medical Research Council (NHMRC) Fellowship Scheme.

**BLSA**. *Baltimore Longitudinal Study of Aging*. The BLSA was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

**BMES**. *Blue Mountains Eye Study*. The BMES has been supported by the Australian RADGAC grant (1992-94) and Australian National Health & Medical Research Council, Canberra Australia (Grant Nos: 974159, 211069, 991407, 457349). The GWAS studies of Blue Mountains Eye Study population are supported by the Australian National Health & Medical Research Council (Grant Nos: 512423, 475604, 529912) and the Wellcome Trust, UK (2008). EGH and JJW are funded by the Australian National Health & Medical Research Council Fellowship Schemes.

**Bus Santé study**. This research was conducted in part using data and resources from the Bus Santé study of the Geneva University Hospitals. This work was partially supported by the Geneva University Hospitals, the Canton of Geneva (Switzerland), the General Directorate of Health (Canton of Geneva), the Swiss School of Public Health Plus (SSPH+) and the Swiss Foundation for Science (Contract No.495 33CM30-124087). Data on creatinine was founded by the Loterie Romande. The investigators of the Bus Santé study thank all the collaborators of the Unit of Population Epidemiology, and Abbott Diagnostics (Baar, Switzerland). We thank Dr Olivier Golaz and Dr Pierre Lescuyer, Geneva University Hospitals.

**CARDIA**. *Coronary Artery Risk in Young Adults*. University of Alabama at Birmingham (N01-HC-48047), University of Minnesota (N01-HC-48048), Northwestern University (N01-HC-48049), Kaiser Foundation Research Institute (N01-HC-48050), University of Alabama at Birmingham (N01-HC-95095), Tufts-New England Medical Center (N01-HC-45204), Wake Forest University (N01-HC-45205), Harbor-UCLA Research and Education Institute (N01-HC-05187), University of California, Irvine (N01-HC-45134, N01-HC-95100).

**CHS**. *Cardiovascular Health Study*. The CHS research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant numbers U01 HL080295 and R01 HL087652 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

**CROATIA-KORCULA**. The Korcula study in the Croatian island of Vis was supported through the grants from the Medical Research Council UK to H.C., A.F.W. and I.R.; and Ministry of Science, Education and Sport of the Republic of Croatia to I.R. (number 108-1080315-0302) . We would like to acknowledge the contributions of the recruitment team in Korcula, the administrative teams in Croatia and Edinburgh (Rosa Bisset) and the people of Korcula.

**CROATIA-SPLIT**. The CROATIA-Split study was supported through the grants from the Medical Research Council UK.;and Ministry of Science, Education and Sport of the Republic of Croatia. (number 108-1080315-0302). We would like to acknowledge the invaluable contributions of the recruitment team from the Croatian Centre for Global Health, University of Split, the administrative teams in Croatia and Edinburgh and the people of Split. The SNP genotyping for the SPLIT cohort was performed by AROS Applied Biotechnology, Aarhus, Denmark.

**CROATIA-VIS**. The Vis study in the Croatian island of Vis was supported through the grants from the Medical Research Council UK to H.C., A.F.W. and I.R.; and Ministry of Science, Education and Sport of the Republic of Croatia to I.R. (number 108-1080315-0302) and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). We would like to acknowledge the invaluable contributions of the recruitment

team (including those from the Institute of Anthropological Research in Zagreb) in Vis, the administrative teams in Croatia and Edinburgh (Rosa Bisset) and the people of Vis.

**DESIR**. *Data from an Epidemiological Study on the Insulin Resistance syndrome*. DESIR genetic data was supported in part by the “Conseil Regional Nord-Pas-de-Calais: Fonds européen de développement économique et regional (CPER 2011-2013); Genome Quebec-Genome Canada; and the British Medical Research Council.

**EGCUT**. *Estonian Genome Center University of Tartu*. EGCUT received financing from FP7 grants (278913, 306031, 313010) and targeted financing from Estonian Government (SF0180142s08). EGCUT studies were covered from Infra-structure grant no. 3.2.0304.11-0312 funded mostly by the European Regional Development Fund, Center of Excellence in Genomics (EXCEGEN) and University of Tartu (SP1GVARENG). We acknowledge EGCUT technical personnel, especially Mr V. Soo and S. Smit. Data analyses were carried out in part in the High Performance Computing Center of the University of Tartu.

**ERF**. *Erasmus Rucphen Family study*. The ERF study was supported by grants from the Netherlands Organization for Scientific Research (NWO; Pioneergrant), Erasmus Medical Center, the Centre for Medical Systems Biology (CMSB), and the Netherlands Kidney Foundation. We are grateful to all patients and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, Jeannette Vergeer for the supervision of the laboratory work and P. Snijders for his help in data collection.

**ESTHER**. *Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten THerapie chronischer ERkrankungen in der älteren Bevölkerung*. We thank all the individuals who took part in this study and all the researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out.This work was supported in part by the Baden-Württemberg State Ministry of Science, Research and Arts; by the German Federal Ministry of Education and Research (grant number 01ET0717); and by the CHANCES project funded in the Seventh Framework Programme of the Directorate-General for Research and Innovation in the European Commission (grant number 242244).

**FamHS**. *Family Heart Study*. The FHS work was supported in part by NIH grants 5R01HL08770003, 5R01HL08821502 (Michael A.Province) from the NHLBI and 5R01DK07568102, 5R01DK06833603 from the NIDDK (I.B.B.). The authors thank the staff and participants of the FamHS for their important contributions.

**FHS**. *Framingham Heart Study*. This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center.

**GENDIAN**. *GENetics of DIAbetic Nephropathy study*. The support of the physicians, the patients, and the staff of the Diabetes Zentrum Mergentheim (Head: Prof. Dr. Thomas Haak), the diabetes outpatient clinic Dr Nusser - Dr Kreisel, the dialysis centers KfH Amberg, KfH Bayreuth, KfH Deggendorf, KfH Donauwörth, KfH Freising, KfH Freyung, KfH Fürth, KfH Hof, KfH Ingolstadt, KfH Kelheim, KfH München Elsenheimerstraße, KfH München-Schwabing, KfH Neumarkt, KfH Neusäß, KfH Oberschleißheim, KfH Passau, KfH Plauen, KfH Regensburg Günzstraße, KfH Regensburg Caritas-Krankenhaus, KfH Straubing, KfH Sulzbach-Rosenberg, KfH Weiden, Dialysezentrum Augsburg Dr. Kirschner, Dialysezentrum Bad Alexandersbad, KfH Bamberg, Dialysezentrum Emmering, Dialysezentrum Klinikum Landshut, Dialysezentrum Landshut, Dialysezentrum Pfarrkirchen, Dialysezentrum Schwandorf, Dr. Angela Götz, the medical doctoral student Johanna Christ and the Study Nurse Ingrid Lugauer. The expert technical assistance of Claudia Strohmeier is acknowledged. Phenotyping was funded by the Dr. Robert Pfleger-Stiftung (Dr Carsten A. Böger), the MSD Stipend Diabetes (Dr Carsten A. Böger) and the University Hospital of Regensburg (intramural grant ReForM A to Dr. A. Götz, ReForM C to Dr. Carsten Böger). Genome-wide genotyping was funded by the KfH Stiftung Präventivmedizin e.V. (Dr. Carsten A. Böger, Dr. Jens Brüning), the Else Kröner-Fresenius-Stiftung (2012_A147 to Dr Carsten A. Böger and Dr Iris M. Heid) and the University Hospital Regensburg (Dr Carsten A. Böger). Data analysis was funded by the Else Kröner-Fresenius Stiftung (Dr. Iris M. Heid and Dr. Carsten A. Böger: 2012_A147; Dr. Carsten A. Böger and Dr. Bernhard K. Krämer: P48/08//A11/08). GENDIAN Study Group: Mathias Gorski, Iris M. Heid, Bernhard K. Krämer, Myriam Rheinberger, Michael Broll, Alexander Lammert, Jens

Brüning, Matthias Olden, Klaus Stark, Claudia Strohmeier, Simone Neumeier, Sarah Hufnagel, Petra Jackermeier, Emilia Ruff, Johanna Christ, Peter Nürnberg, Thomas Haak, Carsten A. Böger.

**GENOA**. *Genetic Epidemiology Network Of Arteriopathy*. This research was partially supported by the National Heart Lung and Blood Institute of the National Institutes of Health R01 HL-87660.

**GHS**. *Gutenberg Heart Study*. The Gutenberg Health study is funded through the government of Rheinland-Pfalz (No. AZ 961-386261/733), the research program “Wissen schafft Zukunft” and the “Schwerpunkt Vaskuläre Prävention” of the Johannes Gutenberg University of Mainz and its contract with Boehringer Ingelheim and PHILIPS medical systems, including an unrestricted grant for the Gutenberg Health Study. Further, this project has been supported by the National Genome Network “NGFNplus” by the federal Ministry of Education and Research, Germany (No. 01GS0833 and 01GS0831, projects A3/D1).

**GSK** cases/controls. Funding Source: Max-Planck Society, German Federal Ministry of Education and Research (BMBF) in the framework of the National Genome Research Network (NGFN), Foerderkennzeichen 01GS0481.

**HABC**. *Health Aging and Body Composition Study*. The HABC study was funded by the National Institutes of Aging. This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

**HANDLS**. This research was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (Intramural Project # Z01-AG000513 and human subjects protocol # 2009-149). Data analyses for the HANDLS study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov).

**HCS**. *Hunter Community Study*. The University of Newcastle provided $300,000 from its Strategic Initiatives Fund, and $600,000 from the Gladys M Brawn Senior Research Fellowship scheme; Vincent Fairfax Family Foundation, a private philanthropic trust, provided $195,000; The Hunter Medical Research Institute provided media support during the initial recruitment of participants; and Dr Anne Crotty, Prof. Rodney Scott and Associate Prof. Levi provided financial support towards freezing costs for the long-term storage of participant blood samples. The authors would like to thank the men and women participating in the HCS as well as all the staff, investigators and collaborators who have supported or been involved in the project to date. A special thank you should go to Alison Koschel and Debbie Quain who were instrumental in setting up the pilot study and initial phase of the project.

**HPFS**. *Health Professionals Follow-Up Study.* The NHS/HPFS type 2 diabetes GWAS (U01HG004399) is a component of a collaborative project that includes 13 other GWAS (U01HG004738, U01HG004422, U01HG004402, U01HG004729, U01HG004726, U01HG004735, U01HG004415, U01HG004436, U01HG004423, U01HG004728, RFAHG006033; National Institute of Dental & Craniofacial Research: U01DE018993, U01DE018903) funded as part of the Gene Environment-Association Studies (GENEVA) under the NIH Genes, Environment and Health Initiative (GEI). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Genotyping was performed at the Broad Institute of MIT and Harvard, with funding support from the NIH GEI (U01HG04424), and Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438) and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease”(HHSN268200782096C). Additional funding for the current research was provided by the National Cancer Institute (P01CA087969, P01CA055075), and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK058845). We thank the staff and participants of the NHS and HPFS for their dedication and commitment.

**HUFS**. The *Howard University Family Study* was supported by National Institutes of Health grants S06GM008016-320107 and S06GM008016-380111. Enrollment was carried out at the Howard University General Clinical Research Center, supported by National Institutes of Health grant 2M01RR010284. This research was supported in part by the

Intramural Research Program of the Center for Research on Genomics and Global Health. The Center for Research on Genomics and Global Health is supported by the National Human Genome Research Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Center for Information Technology, and the Office of the Director at the National Institutes of Health (Z01HG200362). Genotyping support was provided by the Coriell Institute for Medical Research. We thank the participants of the Howard University Family Study. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health.

**HYPERGENES**. *European Network for Genetic-Epidemiological Studies: building a method to dissect complex genetic traits, using essential hypertension as a disease model*. HYPERGENES (FP7 - HEALTH-F4-2007-201550); INTEROMICS (MIUR - CNR Italian Flagship Project); IC15-CT98-0329-EPOGH, LSHM-CT-2006-037093; HEALTH-2011-278249-EU-MASCARA, and ERC Advanced Grant-2011-294713-EPLORE and the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium (grants G.0575.06 and G.0734.09).

Patricia B. Munroe's work forms part of the research themes contributing to the translational research portfolio for the NIHR Barts Cardiovascular Biomedical Research Unit.

**INCIPE**. The INCIPE study was co-sponsored by Fondazione Cassa di Risparmio di Verona, Azienda Ospedaliera di Verona, and University of Verona, Italy.

**INGI-CARLANTINO**. *Italian Network on Genetic Isolates – Carlantino.* We thank Anna Morgan and Angela D'Eustacchio for technical support. We are grateful to the municipal administrators for their collaboration on the project and for logistic support. We would like to thank all participants to this study.

**INGI-CILENTO**. *Italian Network on Genetic Isolates – Cilento.* We thank the populations of Cilento for their participation in the study. This work was supported by grants from the EU (Vasoplus-037254), the Italian Ministry of Universities (FIRB -RBIN064YAT), the Assessorato Ricerca Regione Campania, the Ente Parco Nazionale del Cilento e Vallo di Diano and the Fondazione Banco di Napoli to MC.

**INGI-FVG.** *Italian Network on Genetic Isolates – Friuli Venezia-Giulia.* We thank Anna Morgan and Angela D'Eustacchio for technical support. We are grateful to the municipal administrators for their collaboration on the project and for logistic support. We would like to thank all participants to this study.

**INGI-VAL BORBERA**.*Italian Network on Genetic Isolates – Val Borbera*. The research was done using data obtained thanks to funds from Compagnia di San Paolo, Torino, Italy, Cariplo Fundation, Milano, Italy and Italian Ministry of Health Progetto Finalizzato 2007 and 2009.

**IPM**. *Mount Sinai BioMe Biobank Program*. The Mount Sinai BioMe Biobank Program is supported by The Andrea and Charles Bronfman Philanthropies.

**JHS**. *Jackson Heart Study*. Jackson State University (N01-HC-95170), University of Mississippi (N01-HC-95171), Tougaloo College (N01-HC-95172).

**JUPITER**. We thank Jean MacFadyen, Lynda Rose, the JUPITER study participants and the >1000 physicians worldwide for their personal time, effort and commitment to JUPITER. This work was supported by research funds from AstraZeneca to Drs. Ridker and Chasman.

**HRS**. *Health and Retirement Study*. HRS is supported by the National Institute on Aging (NIA U01AG009740). The genotyping was funded as a separate award from the National Institute on Aging (RC2 AG036495). Our genotyping was conducted by the NIH Center for Inherited Disease Research (CIDR) at Johns Hopkins University. Genotyping quality control and final preparation of the data were perfomed by the Genetics Coordinating Center at the University of Washington.

**KORA F3** and **F4**. The genetic epidemiological work was funded by the NIH subcontract from the Children's Hospital, Boston, US, (H.E.W., I.M.H, prime grant 1 R01 DK075787-01A1), the German National Genome Research Net NGFN2 and NGFNplus (H.E.W. 01GS0823; WK project A3, number 01GS0834), the Munich Center of Health

Sciences (MC Health) as part of LMUinnovativ, and by the Else Kröner-Fresenius-Stiftung (P48/08//A11/08; C.A.B., B.K.K; 2012_A147 to CAB and IMH.). The kidney parameter measurements in F3 were funded by the Else Kröner-Fresenius-Stiftung (C.A.B., B.K.K.) and the Regensburg University Medical Center, Germany; in F4 by the University of Ulm, Germany (W.K.). Genome wide genotyping costs in F3 and F4 were in part funded by the Else Kröner-Fresenius-Stiftung (C.A.B., B.K.K.). Denovo genotyping in F3 and F4 were funded by the Else Kröner-Fresenius-Stiftung (C.A.B., B.K.K.). The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, by the German Federal Ministry of Education and Research and by the State of Bavaria. Genotyping was performed in the Genome Analysis Center (GAC) of the Helmholtz Zentrum München. The LINUX platform for computation were funded by the University of Regensburg for the Department of Epidemiology and Preventive Medicine at the Regensburg University Medical Center.

**LURIC.** *Ludwigshafen Risk and Cardiovascular Health Study*. We extend our appreciation to the participants of the LURIC study; without their collaboration, this article would not have been written. We thank the LURIC study team who were either temporarily or permanently involved in patient recruitment as well as sample and data handling, in addition to the laboratory staff at the Ludwigshafen General Hospital and the Universities of Freiburg and Ulm, Germany. LURIC has received funding from the 6th Framework Program (integrated project Bloodomics, grant LSHM-CT-2004-503485) and 7th Framework Program (Atheroremo, grant agreement number 201668 and RiskyCAD, grant agreement number 305739) of the European Union.

**MESA**. *Multi-Ethnic Study of Atherosclerosis*. University of Washington (N01-HC-95159),Regents of the University of California (N01-HC-95160), Columbia University (N01-HC-95161), Johns Hopkins University (N01-HC-95162, N01-HC-95168), University of Minnesota (N01-HC-95163), Northwestern University (N01-HC-95164), Wake Forest University (N01-HC-95165), University of Vermont (N01-HC-95166), New England Medical Center (N01-HC-95167), Harbor-UCLA Research and Education Institute (N01-HC-95169), Cedars-Sinai Medical Center (R01-HL-071205), University of Virginia (subcontract to R01-HL-071205)

**MICROS**. *Microisolates in South Tyrol study*. We owe a debt of gratitude to all participants. We thank the primary care practitioners Raffaela Stocker, Stefan Waldner, Toni Pizzecco, Josef Plangger, Ugo Marcadent and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project. We thank Dr. Peter Riegler (Hemodialysis Unit, Hospital of Merano) for the important discussions. In South Tyrol, the study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano, the South Tyrolean Sparkasse Foundation, and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947).

**NESDA**. *The Netherlands Study of Depression and Anxiety*. The infrastructure for the NESDA is funded through the Geestkracht programme of the Dutch Scientific Organization (ZON-MW, grant number 10-000-1002) and matching funds from participating universities and mental health care organizations. Genotyping in NESDA was funded by the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health. Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (I 480-05-003) along with a supplement from the Dutch Brain Foundation.

**NHS**. *Nurses' Health Study*. The NHS/HPFS type 2 diabetes GWAS (U01HG004399) is a component of a collaborative project that includes 13 other GWAS (U01HG004738, U01HG004422, U01HG004402, U01HG004729, U01HG004726, U01HG004735, U01HG004415, U01HG004436, U01HG004423, U01HG004728, RFAHG006033; National Institute of Dental & Craniofacial Research: U01DE018993, U01DE018903) funded as part of the Gene Environment-Association Studies (GENEVA) under the NIH Genes, Environment and Health Initiative (GEI). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Genotyping was performed at the Broad Institute of MIT and Harvard, with funding support from the NIH GEI (U01HG04424), and Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438) and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease"(HHSN268200782096C). The NHS renal function and

albuminuria work was supported by DK66574. Additional funding for the current research was provided by the National Cancer Institute (P01CA087969, P01CA055075), and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK058845). We thank the staff and participants of the NHS and HPFS for their dedication and commitment.

**NSPHS**. *The Northern Swedish Population Health Study*. The NSPHS was supported by grants from the Swedish Natural Sciences Research Council, the European Union through the EUROSPAN project (contract no. LSHG-CT-2006-018947), the Foundation for Strategic Research (SSF) and the Linneaus Centre for Bioinformatics (LCB). We are also grateful for the contribution of samples from the Medical Biobank in Umeå and for the contribution of the district nurse Svea Hennix in the Karesuando study.

**OGP** (*Ogliastra Genetic Park*) including **OGP-TALANA**. We thank the Ogliastra population and all the individuals who participated in this study. We are grateful to the municipal administrators for their collaboration to the project and for economic and logistic support. This work was supported by grants from the Italian Ministry of Education, University and Research (MIUR) no.5571/DSPAR/2002 and (FIRB) D. M. no. 718/Ric/2005.

**ORCADES**. *Orkney Complex Disease Study*. ORCADES was supported by the the Chief Scientist Office of the Scottish Government , the Royal Society and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We would like to acknowledge the invaluable contributions of Lorraine Anderson, the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney.

**POPGEN**. The POPGen study was supported by the German Ministry of Education and Research (BMBF) through the National Genome Research Network (NGFN). It is currently funded by the Ministry of Science, Commerce and Transportation of the State of Schleswig-Holstein. The project has also received infrastructure support through the DFG excellence cluster “Inflammation at Interfaces” and the BMBF funded project P2N (01EY1103).

**PREVEND**. *Prevention of Renal and Vascular Endstage Disease Study*. PREVEND genetics is supported by the Dutch Kidney Foundation (Grant E033), the EU project grant GENECURE (FP-6 LSHM CT 2006 037697), the National Institutes of Health (grant 2R01LM010098), The Netherlands organisation for health research and development (NWO-Groot grant 175.010.2007.006, NWO VENI grant 916.761.70, ZonMw grant 90.700.441), and the Dutch Inter University Cardiology Institute Netherlands (ICIN).

**PROSPER-PHASE**. *Prospective Study of Pravastatin in the Elderly at Risk*. The PROSPER trial was supported by an investigator initiated grant from Bristol-Myers Squibb, USA. The study was conducted, analysed, and reported independently of the company.

**RS-I** and **II**. *The Rotterdam Study*. The GWA study was funded by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Consortium for Healthy Aging (NCHA) project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Dr Michael Moorhouse, Marijn Verkerk, and Sander Bervoets for their help in creating the GWAS database. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are very grateful to the participants and staff from the Rotterdam Study, the participating general practioners and the pharmacists. We would like to thank Dr. Tobias A. Knoch, Luc V. de Zeeuw, Anis Abuseiris, and Rob de Graaf as well as their institutions the Erasmus Computing Grid, Rotterdam, The Netherlands, and especially the national German MediGRID and Services@MediGRID part of the German D-Grid, both funded by the German Bundesministerium fuer Forschung und Technology under grants #01 AK 803 A-H and # 01 IG 07015 G, for access to their grid resources. Abbas Dehghan is supported by NWO grant (vici, 918-76-619).

**SAPALDIA**. *Swiss Study on Air Pollution and Lung Diseases in Adults*. The SAPALDIA Team: Study directorate: T Rochat (p), NM Probst Hensch (e/g), N Künzli (e/exp), C Schindler (s), JM Gaspoz (c) Scientific team: JC Barthélémy (c), W Berger (g), R Bettschart (p), A Bircher (a), O Brändli (p), C Brombach (n), M Brutsche (p), L Burdet (p), M Frey (p), U Frey (pd), MW Gerbase (p), D Gold (e/c/p), E de Groot (c), W Karrer (p), R Keller (p), B Martin (pa), D Miedinger (o), U Neu (exp), L Nicod (p), M Pons (p), F Roche (c), T Rothe (p), E Russi (p), P Schmid-Grendelmeyer

(a), A Schmidt-Trucksäss (pa), A Turk (p), J Schwartz (e), D. Stolz (p), P Straehl (exp), JM Tschopp (p), A von Eckardstein (cc), E Zemp Stutz (e). Scientific team at coordinating centers: M Adam (e/g), C Autenrieth (pa), PO Bridevaux (p), D Carballo (c), E Corradi (exp), I Curjuric (e), J Dratva (e), A Di Pasquale (s), E Dupuis Lozeron (s), E Fischer (e), M Germond (s), L Grize (s), D Keidel (s), S Kriemler (pa), A Kumar (g), M Imboden (g), N Maire (s), A Mehta (e), H Phuleria (exp), E Schaffner (s), GA Thun (g) A Ineichen (exp), M Ragettli (e), M Ritter (exp), T Schikowski (e), M Tarantino (s), M Tsai (exp) (a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics. Funding: The Swiss National Science Foundation (grants no 33CSCO-134276/1, 33CSCO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099), the Federal Office for Forest, Environment and Landscape, the Federal Office of Public Health, the Federal Office of Roads and Transport, the canton's government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais, and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/ Basel Landschaft, Geneva, Ticino, Valais and Zurich, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission 018996 (GABRIEL), Wellcome Trust WT 084703MA. The study could not have been done without the help of the study participants, technical and administrative support and the medical teams and field workers at the local study sites. Local fieldworkers : Aarau: S Brun, G Giger, M Sperisen, M Stahel, Basel: C Bürli, C Dahler, N Oertli, I Harreh, F Karrer, G Novicic, N Wyttenbacher, Davos: A Saner, P Senn, R Winzeler, Geneva: F Bonfils, B Blicharz, C Landolt, J Rochat, Lugano: S Boccia, E Gehrig, MT Mandia, G Solari, B Viscardi, Montana: AP Bieri, C Darioly, M Maire, Payerne: F Ding, P Danieli A Vonnez, Wald: D Bodmer, E Hochstrasser, R Kunz, C Meier, J Rakic, U Schafroth, A Walder. Administrative staff: C Gabriel, R Gutknecht.

**SAPHIR**. *Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk*. The SAPHIR-study was partially supported by a grant from the Kamillo Eisner Stiftung to B. Paulweber and by grants from the "Genomics of Lipid-associated Disorders – GOLD" of the "Austrian Genome Research Programme GEN-AU" to F. Kronenberg.

**SHIP** and **SHIP-TREND**. *The Study of Health in Pomerania*. SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG and the Caché Campus program of the InterSystems GmbH. The SHIP authors are grateful to Mario Stanke for the opportunity to use his Server Cluster for the SNP imputation as well as to Holger Prokisch and Thomas Meitinger (Helmholtz Zentrum München) for the genotyping of the SHIP-TREND cohort.

**SIGNET-Sea Islands** and **SIGNET-REGARDS**. The *Sea Islands Genetics Network* is supported by R01 DK084350 (M Sale), and consists of data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort (U01 NS041588; G Howard), Project SuGAR (Sea Islands Genetic African American Registry; W.M. Keck Foundation; WT Garvey), and a South Carolina Center of Biomedical Research Excellence (COBRE) for Oral Health Project P20-RR-17696 (JK Fernandes).

**SKIPOGH**. *The Swiss Kidney Project on Genes in Hypertension.* This research was funded by a grant from the Swiss National Science Foundation (33CM30-124087). The study also received support from Lausanne University Hospital, Geneva University Hospital and Bern University Hospital, Switzerland. Murielle Bochud received support from the Swiss School of Public Health Plus (SSPH+).

**SORBS**. *The Sorbs study*. This work was supported by grants from the German Research Council (SFB- 1052 "Obesity mechanisms" to Michael Stumvoll, Anke Tönjes and Peter Kovacs), from the German Diabetes Association (to Anke Tönjes and Peter Kovacs) and from the DHFD (Diabetes Hilfs- und Forschungsfonds Deutschland to Michael Stumvoll and Peter Kovacs). IFB AdiposityDiseases is supported by the Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1001. We thank all those who participated in the study. Sincere thanks are

given to Knut Krohn (Microarray Core Facility of the Interdisciplinary Centre for Clinical Research, University of Leipzig) for the genotyping support.

**Vanderbilt**. Illumina HumanOmni1-Quad and Illumina HumanOmni5-Quad genoytping were supported by NIGMS RC2-GM092318. Illumina Human660W-Quad genotyping was supported by the eMERGE Network, initiated and funded by the National Human Genome Research Institute, with additional funding from the National Institute of General Medical Sciences (NIGMS), through U01-HG04603.

**WGHS**. *Women's Genome Health Study*. The WGHS is supported by HL 043851 and HL69757 from the National Heart, Lung, and Blood Institute and CA 047988 from the National Cancer Institute, the Donald W. Reynolds Foundation and the Fondation Leducq, with collaborative scientific support and funding for genotyping provided by Amgen.

**YFS**. *Young Finns Study*. The YFS has been financially supported by the Academy of Finland: grants 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi), the Social Insurance Institution of Finland, Kuopio, Tampere and Turku University Hospital Medical Funds (grant 9M048 and 9N035 for TeLeht), Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research and Finnish Cultural Foundation, Tampere Tuberculosis Foundation and Emil Aaltonen Foundation (T.L). The expert technical assistance in the statistical analyses by Ville Aalto and Irina Lisinen is acknowledged.

## References


1. Freedman, M. L. *et al*. Assessing the impact of population stratification on genetic association studies. *Nat. Genet.* **36**, 388-393 (2004).
2. de Bakker, P. I. *et al*. Practical aspects of imputation-driven meta-analysis of genome-wide association studies. *Hum. Mol. Genet.* **17**, R122-8 (2008).
3. Pattaro, C. *et al*. Genome-wide association and functional follow-up reveals new loci for kidney function. *PLoS Genet.* **8**, e1002584 (2012).
4. Kottgen, A. *et al*. New loci associated with kidney function and chronic kidney disease. *Nat. Genet.* **42**, 376-384 (2010).
5. Kottgen, A. *et al*. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat. Genet.* **41**, 712-717 (2009).
6. Chasman, D. I. *et al*. Integration of genome-wide association studies with biological knowledge identifies six novel genes related to kidney function. *Hum. Mol. Genet.* **21**, 5329-5343 (2012).
7. Johnson, A. D. *et al*. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics* **24**, 2938-2939 (2008).
8. Schunkert, H. *et al*. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat. Genet.* **43**, 333-338 (2011).
9. Vasan, R. S. *et al*. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. *JAMA* **302**, 168-178 (2009).
10. Smith, N. L. *et al*. Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium. *Circ. Cardiovasc. Genet.* **3**, 256-266 (2010).
11. International Consortium for Blood Pressure Genome-Wide Association Studies *et al*. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **478**, 103-109 (2011).
12. Dupuis, J. *et al*. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat. Genet.* **42**, 105-116 (2010).
13. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* **43**, 969-976 (2011).
14. Berndt, S. I. *et al*. Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat. Genet.* **45**, 501-512 (2013).
15. Thorleifsson, G. *et al*. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat. Genet.* **41**, 18-24 (2009).
16. Speliotes, E. K. *et al*. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **42**, 937-948 (2010).
17. Jostins, L. *et al*. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* **491**, 119-124 (2012).
18. Mells, G. F. *et al*. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. *Nat. Genet.* **43**, 329-332 (2011).
19. Okada, Y. *et al*. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. *Nat. Genet.* **44**, 904-909 (2012).
20. Kottgen, A. *et al*. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat. Genet.* **45**, 145-154 (2013).
21. Paternoster, L. *et al*. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. *Nat. Genet.* **44**, 187-192 (2011).
22. Teslovich, T. M. *et al*. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707-713 (2010).
23. Yang, Q. *et al*. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ. Cardiovasc. Genet.* **3**, 523-530 (2010).
24. van Meurs, J. B. *et al*. Common genetic loci influencing plasma homocysteine concentrations and their effect on risk of coronary artery disease. *Am. J. Clin. Nutr.* **98**, 668-676 (2013).
25. Barrett, J. H. *et al*. Genome-wide association study identifies three new melanoma susceptibility loci. *Nat. Genet.* **43**, 1108-1113 (2011).
26. Bishop, D. T. *et al*. Genome-wide association study identifies three loci associated with melanoma risk. *Nat. Genet.* **41**, 920-925 (2009).
27. Han, J. *et al*. A genome-wide association study identifies novel alleles associated with hair color and skin pigmentation. *PLoS Genet.* **4**, e1000074 (2008).
28. Zhang, M. *et al*. Genome-wide association studies identify several new loci associated with pigmentation traits and skin cancer risk in European Americans. *Hum. Mol. Genet.* **22**, 2948-2959 (2013).
29. Nan, H. *et al*. Genome-wide association study identifies novel alleles associated with risk of cutaneous basal cell carcinoma and squamous cell carcinoma. *Hum. Mol. Genet.* **20**, 3718-3724 (2011).

30. Sulem, P. *et al*. Genetic determinants of hair, eye and skin pigmentation in Europeans. *Nat. Genet.* **39**, 1443-1452 (2007).
31. Siddiq, A. *et al*. A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. *Hum. Mol. Genet.* **21**, 5373-5384 (2012).
32. Sulem, P. *et al*. Two newly identified genetic determinants of pigmentation in Europeans. *Nat. Genet.* **40**, 835-837 (2008).
33. Brown, K. M. *et al*. Common sequence variants on 20q11.22 confer melanoma susceptibility. *Nat. Genet.* **40**, 838-840 (2008).
34. Morris, A. P. Transethnic meta-analysis of genomewide association studies. *Genet. Epidemiol.* **35**, 809-822 (2011).
35. Zhang, B. *et al*. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* **153**, 707-720 (2013).
36. Greenawalt, D. M. *et al*. A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. *Genome Res.* **21**, 1008-1016 (2011).
37. Schadt, E. E. *et al*. Mapping the genetic architecture of gene expression in human liver. *PLoS Biol.* **6**, e107 (2008).
38. Innocenti, F. *et al*. Identification, replication, and functional fine-mapping of expression quantitative trait loci in primary human liver tissue. *PLoS Genet.* **7**, e1002078 (2011).
39. Schroder, A. *et al*. Genomics of ADME gene expression: mapping expression quantitative trait loci relevant for absorption, distribution, metabolism and excretion of drugs in human liver. *Pharmacogenomics J.* **13**, 12-20 (2013).
40. Fehrmann, R. S. *et al*. Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA. *PLoS Genet.* **7**, e1002197 (2011).
41. Grundberg, E. *et al*. Mapping cis- and trans-regulatory effects across multiple tissues in twins. *Nat. Genet.* **44**, 1084-1089 (2012).
42. Dimas, A. S. *et al*. Common regulatory variation impacts gene expression in a cell type-dependent manner. *Science* **325**, 1246-1250 (2009).
43. Zeller, T. *et al*. Genetics and beyond--the transcriptome of human monocytes and disease susceptibility. *PLoS One* **5**, e10693 (2010).
44. Emilsson, V. *et al*. Genetics of gene expression and its effect on disease. *Nature* **452**, 423-428 (2008).
45. Hao, K. *et al*. Lung eQTLs to help reveal the molecular underpinnings of asthma. *PLoS Genet.* **8**, e1003029 (2012).
46. Kabakchiev, B. & Silverberg, M. S. Expression quantitative trait loci analysis identifies associations between genotype and gene expression in human intestine. *Gastroenterology* **144**, 1488-96, 1496.e1-3 (2013).
47. Liang, L. *et al*. A cross-platform analysis of 14,177 expression quantitative trait loci derived from lymphoblastoid cell lines. *Genome Res.* **23**, 716-726 (2013).
48. Degner, J. F. *et al*. DNase I sensitivity QTLs are a major determinant of human expression variation. *Nature* **482**, 390-394 (2012).
49. Li, Q. *et al*. Integrative eQTL-based analyses reveal the biology of breast cancer risk loci. *Cell* **152**, 633-641 (2013).
50. Zou, F. *et al*. Brain expression genome-wide association study (eGWAS) identifies human disease-associated variants. *PLoS Genet.* **8**, e1002707 (2012).
51. Goring, H. H. *et al*. Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes. *Nat. Genet.* **39**, 1208-1216 (2007).
52. Zhu, M. *et al*. Beta-mannosidosis mice: a model for the human lysosomal storage disease. *Hum. Mol. Genet.* **15**, 493-500 (2006).
53. Gill, P. S. & Rosenblum, N. D. Control of murine kidney development by sonic hedgehog and its GLI effectors. *Cell. Cycle* **5**, 1426-1430 (2006).
54. Lu, B. C. *et al*. Etv4 and Etv5 are required downstream of GDNF and Ret for kidney branching morphogenesis. *Nat. Genet.* **41**, 1295-1302 (2009).
55. Kozak, E. M. & Tate, S. S. Glutathione-degrading enzymes of microvillus membranes. *J. Biol. Chem.* **257**, 6322-6327 (1982).
56. Campbell, B. J., Forrester, L. J., Zahler, W. L. & Burks, M. Beta-lactamase activity of purified and partially characterized human renal dipeptidase. *J. Biol. Chem.* **259**, 14586-14590 (1984).
57. Mazumder, B. *et al*. Regulated release of L13a from the 60S ribosomal subunit as a mechanism of transcript-specific translational control. *Cell* **115**, 187-198 (2003).
58. Koppen, M., Metodiev, M. D., Casari, G., Rugarli, E. I. & Langer, T. Variable and tissue-specific subunit composition of mitochondrial m-AAA protease complexes linked to hereditary spastic paraplegia. *Mol. Cell. Biol.* **27**, 758-767 (2007).
59. Elleuch, N. *et al*. Mutation analysis of the paraplegin gene (SPG7) in patients with hereditary spastic paraplegia. *Neurology* **66**, 654-659 (2006).
60. Arnoldi, A. *et al*. A clinical, genetic, and biochemical characterization of SPG7 mutations in a large cohort of patients with hereditary spastic paraplegia. *Hum. Mutat.* **29**, 522-531 (2008).

61. Sanchez-Ferrero, E. *et al*. SPG7 mutational screening in spastic paraplegia patients supports a dominant effect for some mutations and a pathogenic role for p.A510V. *Clin. Genet.* **83**, 257-262 (2013).
62. Tekin, M. *et al*. The KBG syndrome: confirmation of autosomal dominant inheritance and further delineation of the phenotype. *Am. J. Med. Genet. A.* **130A**, 284-287 (2004).
63. Sirmaci, A. *et al*. Mutations in ANKRD11 cause KBG syndrome, characterized by intellectual disability, skeletal malformations, and macrodontia. *Am. J. Hum. Genet.* **89**, 289-294 (2011).
64. Li, X. *et al*. Cloning and chromosomal localization of the human and murine genes for the T-cell transcription factors NFATc and NFATp. *Cytogenet. Cell Genet.* **68**, 185-191 (1995).
65. Langworthy, M., Zhou, B., de Caestecker, M., Moeckel, G. & Baldwin, H. S. NFATc1 identifies a population of proximal tubule cell progenitors. *J. Am. Soc. Nephrol.* **20**, 311-321 (2009).
66. Wang, Y. *et al*. Activation of NFAT signaling in podocytes causes glomerulosclerosis. *J. Am. Soc. Nephrol.* **21**, 1657-1666 (2010).
67. Varon, R. *et al*. Partial deficiency of the C-terminal-domain phosphatase of RNA polymerase II is associated with congenital cataracts facial dysmorphism neuropathy syndrome. *Nat. Genet.* **35**, 185-189 (2003).
68. Ahuja, R. *et al*. Interactions of cubilin with megalin and the product of the amnionless gene (AMN): effect on its stability. *Biochem. J.* **410**, 301-308 (2008).
69. Kantarci, S. *et al*. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. *Nat. Genet.* **39**, 957-959 (2007).
70. Attakpa, E. S., Djibril, N. M., Baba-Moussa, F., Yessoufou, G. & Sezan, A. Expression and role of the genes involved in the transport of bile acids in the liver and kidneys in mice. *J. Basic Clin. Physiol. Pharmacol.* **24**, 97-103 (2013).
71. Parr, B. A. & McMahon, A. P. Sexually dimorphic development of the mammalian reproductive tract requires Wnt-7a. *Nature* **395**, 707-710 (1998).
72. Hirata, H. *et al*. Polymorphisms of DNA repair genes are associated with renal cell carcinoma. *Biochem. Biophys. Res. Commun.* **342**, 1058-1062 (2006).
73. Key, M. D., Andres, D. A., Der, C. J. & Repasky, G. A. Characterization of RERG: an estrogen-regulated tumor suppressor gene. *Methods Enzymol.* **407**, 513-527 (2006).
74. Ozaltin, F. *et al*. Disruption of PTPRO causes childhood-onset nephrotic syndrome. *Am. J. Hum. Genet.* **89**, 139-147 (2011).
75. Wharram, B. L. *et al*. Altered podocyte structure in GLEPP1 (Ptpro)-deficient mice associated with hypertension and low glomerular filtration rate. *J. Clin. Invest.* **106**, 1281-1290 (2000).
76. Zwaenepoel, I. *et al*. Ezrin regulates microvillus morphogenesis by promoting distinct activities of Eps8 proteins. *Mol. Biol. Cell* **23**, 1080-1094 (2012).
77. Garrett, S. H. *et al*. Short and long term gene expression variation and networking in human proximal tubule cells when exposed to cadmium. *BMC Med. Genomics* **6 Suppl 1**, S2-8794-6-S1-S2. Epub 2013 Jan 23 (2013).
78. Cheng, S. B. *et al*. Anatomical location and redistribution of G protein-coupled estrogen receptor-1 during the estrus cycle in mouse kidney and specific binding to estrogens but not aldosterone. *Mol. Cell. Endocrinol.* **382**, 950-959 (2014).
79. Prabhushankar, R., Krueger, C. & Manrique, C. Membrane estrogen receptors: their role in blood pressure regulation and cardiovascular disease. *Curr. Hypertens. Rep.* **16**, 408-013-0408-6 (2014).
80. Kurt, A. H. & Buyukafsar, K. Vasoconstriction induced by G1, a G-protein-coupled oestrogen receptor1 (GPER-1) agonist, in the isolated perfused rat kidney. *Eur. J. Pharmacol.* **702**, 71-78 (2013).
81. Barton, M. Position paper: The membrane estrogen receptor GPER--Clues and questions. *Steroids* **77**, 935-942 (2012).
82. Osborne, M. R. *et al*. The reaction of 7,8-dihydro-7,8-dihydroxybenzo (a) pyrene-9,10-oxide with DNA in relation to the benzo (a) pyrene-DNA products isolated from cells. *Chem. Biol. Interact.* **13**, 343-348 (1976).
83. Huang, W. *et al*. High glucose induces activation of NF-kappaB inflammatory signaling through IkappaBalpha sumoylation in rat mesangial cells. *Biochem. Biophys. Res. Commun.* **438**, 568-574 (2013).
84. Pandey, D. *et al*. SUMO1 negatively regulates reactive oxygen species production from NADPH oxidases. *Arterioscler. Thromb. Vasc. Biol.* **31**, 1634-1642 (2011).
85. Zhang, L. *et al*. A high-throughput screen for chemical inhibitors of exocytic transport in yeast. *Chembiochem* **11**, 1291-1301 (2010).
86. Zhang, L., Huang, M. & Harsay, E. A chemical genetic screen for modulators of exocytic transport identifies inhibitors of a transport mechanism linked to GTR2 function. *Eukaryot. Cell.* **9**, 116-126 (2010).
87. Nowak, J. *et al*. The TP53INP2 protein is required for autophagy in mammalian cells. *Mol. Biol. Cell* **20**, 870-881 (2009).
88. Teng, A., Nair, M., Wells, J., Segre, J. A. & Dai, X. Strain-dependent perinatal lethality of Ovol1-deficient mice and identification of Ovol2 as a downstream target of Ovol1 in skin epidermis. *Biochim. Biophys. Acta* **1772**, 89-95 (2007).
89. Lee, S. D. *et al*. TonEBP stimulates multiple cellular pathways for adaptation to hypertonic stress: organic osmolyte-dependent and -independent pathways. *Am. J. Physiol. Renal Physiol.* **300**, F707-15 (2011).
90. Davis, L. K., Rodgers, B. D. & Kelley, K. M. Angiotensin II- and glucose-stimulated extracellular matrix production: mediation by the insulin-like growth factor (IGF) axis in a murine mesangial cell line. *Endocrine* **33**, 32-39 (2008).

91. Fukasawa, H. *et al*. Ubiquitin-dependent degradation of SnoN and Ski is increased in renal fibrosis induced by obstructive injury. *Kidney Int.* **69**, 1733-1740 (2006).
92. Kirk, A., Campbell, S., Bass, P., Mason, J. & Collins, J. Differential expression of claudin tight junction proteins in the human cortical nephron. *Nephrol. Dial. Transplant.* **25**, 2107-2119 (2010).
93. Kugita, M. *et al*. Global gene expression profiling in early-stage polycystic kidney disease in the Han:SPRD Cy rat identifies a role for RXR signaling. *Am. J. Physiol. Renal Physiol.* **300**, F177-88 (2011).
94. Ng, M. C. *et al*. Transferability and fine mapping of type 2 diabetes loci in African Americans: the Candidate Gene Association Resource Plus Study. *Diabetes* **62**, 965-976 (2013).
95. Lim, X. L. *et al*. KCNQ1 SNPS and susceptibility to diabetic nephropathy in East Asians with type 2 diabetes. *Diabetologia* **55**, 2402-2406 (2012).
96. Liu, C. T. *et al*. Genetic association for renal traits among participants of African ancestry reveals new loci for renal function. *PLoS Genet.* **7**, e1002264 (2011).
97. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology* **22**, 316-325 (2003).
98. Lambert, J. C. *et al*. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat. Genet.* **41**, 1094-1099 (2009).
99. Patel, A. *et al*. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* **370**, 829-840 (2007).
100. Harris, T. B. *et al*. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am. J. Epidemiol.* **165**, 1076-1087 (2007).
101. Mitchell, B. D. *et al*. The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. *Am. Heart J.* **155**, 823-828 (2008).
102. Rampersaud, E. *et al*. The association of coronary artery calcification and carotid artery intima-media thickness with distinct, traditional coronary artery disease risk factors in asymptomatic adults. *Am. J. Epidemiol.* **168**, 1016-1023 (2008).
103. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am. J. Epidemiol.* **129**, 687-702 (1989).
104. Schmidt, R. *et al*. Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study (ASPS). *Neuroepidemiology* **13**, 308-313 (1994).
105. Schmidt, R., Fazekas, F., Kapeller, P., Schmidt, H. & Hartung, H. P. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. *Neurology* **53**, 132-139 (1999).
106. Middelberg, R. P. *et al*. Loci affecting gamma-glutamyl transferase in adults and adolescents show age x SNP interaction and cardiometabolic disease associations. *Hum. Mol. Genet.* **21**, 446-455 (2012).
107. Shock, N. W., et al. Normal Human Aging: The Baltimore Longitudinal Study of Aging. *Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.* (1984).
108. Mitchell, P., Smith, W., Attebo, K. & Wang, J. J. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* **102**, 1450-1460 (1995).
109. Attebo, K., Mitchell, P. & Smith, W. Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology* **103**, 357-364 (1996).
110. Leeder, S. R. *et al*. Low hemoglobin, chronic kidney disease, and risk for coronary heart disease-related death: the Blue Mountains Eye Study. *J. Am. Soc. Nephrol.* **17**, 279-284 (2006).
111. Fried, L. P. *et al*. The Cardiovascular Health Study: design and rationale. *Ann. Epidemiol.* **1**, 263-276 (1991).
112. Heard-Costa, N. L. *et al*. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. *PLoS Genet.* **5**, e1000539 (2009).
113. Polasek, O. *et al*. Genome-wide association study of anthropometric traits in Korcula Island, Croatia. *Croat. Med. J.* **50**, 7-16 (2009).
114. Rudan, I. *et al*. "10001 Dalmatians:" Croatia launches its national biobank. *Croat. Med. J.* **50**, 4-6 (2009).
115. Rudan, I., Campbell, H. & Rudan, P. Genetic epidemiological studies of eastern Adriatic Island isolates, Croatia: objective and strategies. *Coll. Antropol.* **23**, 531-546 (1999).
116. Rudan, I. *et al*. Effects of inbreeding, endogamy, genetic admixture, and outbreeding on human health: a (1001 Dalmatians) study. *Croat. Med. J.* **47**, 601-610 (2006).
117. Guder, W. G. *et al*. Multicentre evaluation of an enzymatic method for creatinine determination using a sensitive colour reagent. *J. Clin. Chem. Clin. Biochem.* **24**, 889-902 (1986).
118. Balkau, B. An epidemiologic survey from a network of French Health Examination Centres, (D.E.S.I.R.): epidemiologic data on the insulin resistance syndrome. *Rev. Epidemiol. Sante Publique* **44**, 373-375 (1996).
119. Metspalu, A. The Estonian Genome Project. *Drug Dev. Res.* **62**, 97-101 (2004).
120. Nelis, M. *et al*. Genetic structure of Europeans: a view from the North-East. *PLoS One* **4**, e5472 (2009).
121. Aulchenko, Y. S. *et al*. Linkage disequilibrium in young genetically isolated Dutch population. *Eur. J. Hum. Genet.* **12**, 527-534 (2004).
122. Higgins, M. *et al*. NHLBI Family Heart Study: objectives and design. *Am. J. Epidemiol.* **143**, 1219-1228 (1996).

123. Kannel, W. B., Feinleib, M., McNamara, P. M., Garrison, R. J. & Castelli, W. P. An investigation of coronary heart disease in families. The Framingham offspring study. *Am. J. Epidemiol.* **110**, 281-290 (1979).
124. Feinleib, M., Kannel, W. B., Garrison, R. J., McNamara, P. M. & Castelli, W. P. The Framingham Offspring Study. Design and preliminary data. *Prev. Med.* **4**, 518-525 (1975).
125. Splansky, G. L. *et al*. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am. J. Epidemiol.* **165**, 1328-1335 (2007).
126. Daniels, P. R. *et al*. Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Am. J. Med.* **116**, 676-681 (2004).
127. Turner, S. T. *et al*. Influence of genomic loci on measures of chronic kidney disease in hypertensive sibships. *J. Am. Soc. Nephrol.* **17**, 2048-2055 (2006).
128. Rule, A. D. *et al*. A comparison of serum creatinine-based methods for identifying chronic kidney disease in hypertensive individuals and their siblings. *Am. J. Hypertens.* **19**, 608-614 (2006).
129. McEvoy, M. *et al*. Cohort profile: The Hunter Community Study. *Int. J. Epidemiol.* **39**, 1452-1463 (2010).
130. Qi, L. *et al*. Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. *Hum. Mol. Genet.* **19**, 2706-2715 (2010).
131. Rimm, E. B. *et al*. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet.* **338**, 464-468 (1991).
132. Hu, F. B. *et al*. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch. Intern. Med.* **161**, 1542-1548 (2001).
133. Manson, J. E. *et al*. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* **338**, 774-778 (1991).
134. Lin, J., Hu, F. B. & Curhan, G. Serum adiponectin and renal dysfunction in men with type 2 diabetes. *Diabetes Care* **30**, 239-244 (2007).
135. Salvi, E. *et al*. Genomewide association study using a high-density single nucleotide polymorphism array and case-control design identifies a novel essential hypertension susceptibility locus in the promoter region of endothelial NO synthase. *Hypertension* **59**, 248-255 (2012).
136. Gambaro, G. *et al*. Prevalence of CKD in northeastern Italy: results of the INCIPE study and comparison with NHANES. *Clin. J. Am. Soc. Nephrol.* **5**, 1946-1953 (2010).
137. D'Adamo, P. *et al*. Metabonomics and population studies: age-related amino acids excretion and inferring networks through the study of urine samples in two Italian isolated populations. *Amino Acids* **38**, 65-73 (2010).
138. Tepper, B. J. *et al*. Variation in the bitter-taste receptor gene TAS2R38, and adiposity in a genetically isolated population in Southern Italy. *Obesity (Silver Spring)* **16**, 2289-2295 (2008).
139. Sala, C. *et al*. Variation of hemoglobin levels in normal Italian populations from genetic isolates. *Haematologica* **93**, 1372-1375 (2008).
140. Ciullo, M. *et al*. New susceptibility locus for hypertension on chromosome 8q by efficient pedigree-breaking in an Italian isolate. *Hum. Mol. Genet.* **15**, 1735-1743 (2006).
141. Colonna, V. *et al*. Campora: a young genetic isolate in South Italy. *Hum. Hered.* **64**, 123-135 (2007).
142. Ciullo, M. *et al*. Identification and replication of a novel obesity locus on chromosome 1q24 in isolated populations of Cilento. *Diabetes* **57**, 783-790 (2008).
143. Colonna, V. *et al*. Comparing population structure as inferred from genealogical versus genetic information. *Eur. J. Hum. Genet.* **17**, 1635-1641 (2009).
144. Siervo, M. *et al*. Angiogenesis and biomarkers of cardiovascular risk in adults with metabolic syndrome. *J. Intern. Med.* **268**, 338-347 (2010).
145. Sorice, R. *et al*. Association of a variant in the CHRNA5-A3-B4 gene cluster region to heavy smoking in the Italian population. *Eur. J. Hum. Genet.* **19**, 593-596 (2011).
146. Ruggiero, D. *et al*. Genetics of VEGF serum variation in human isolated populations of cilento: importance of VEGF polymorphisms. *PLoS One* **6**, e16982 (2011).
147. Siervo, M. *et al*. Body mass index is directly associated with biomarkers of angiogenesis and inflammation in children and adolescents. *Nutrition* **28**, 262-266 (2012).
148. Traglia, M. *et al*. Heritability and demographic analyses in the large isolated population of Val Borbera suggest advantages in mapping complex traits genes. *PLoS One* **4**, e7554 (2009).
149. Ridker, P. M. *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* **359**, 2195-2207 (2008).
150. Chasman, D. I. *et al*. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Circ. Cardiovasc. Genet.* **5**, 257-264 (2012).
151. Wichmann, H. E., Gieger, C., Illig, T. & MONICA/KORA Study Group. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* **67 Suppl 1**, S26-30 (2005).
152. Baumeister, S. E. *et al*. Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. *Am. J. Nephrol.* **31**, 222-229 (2010).
153. Bild, D. E. *et al*. Multi-ethnic study of atherosclerosis: objectives and design. *Am. J. Epidemiol.* **156**, 871-881 (2002).

154. Pattaro, C. *et al*. The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. *BMC Med. Genet.* **8**, 29 (2007).
155. Marroni, F., Grazio, D., Pattaro, C., Devoto, M. & Pramstaller, P. Estimates of genetic and environmental contribution to 43 quantitative traits support sharing of a homogeneous environment in an isolated population from South Tyrol, Italy. *Hum. Hered.* **65**, 175-182 (2008).
156. Pattaro, C. *et al*. A meta-analysis of genome-wide data from five European isolates reveals an association of COL22A1, SYT1, and GABRR2 with serum creatinine level. *BMC Med. Genet.* **11**, 41 (2010).
157. Penninx, B. W. *et al*. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int. J. Methods Psychiatr. Res.* **17**, 121-140 (2008).
158. Sullivan, P. F. *et al*. Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. *Mol. Psychiatry* **14**, 359-375 (2009).
159. Colditz, G. A. & Hankinson, S. E. The Nurses' Health Study: lifestyle and health among women. *Nat. Rev. Cancer.* **5**, 388-396 (2005).
160. Lin, J., Fung, T. T., Hu, F. B. & Curhan, G. C. Association of dietary patterns with albuminuria and kidney function decline in older white women: a subgroup analysis from the Nurses' Health Study. *Am. J. Kidney Dis.* **57**, 245-254 (2011).
161. Johansson, A., Vavruch-Nilsson, V., Edin-Liljegren, A., Sjolander, P. & Gyllensten, U. Linkage disequilibrium between microsatellite markers in the Swedish Sami relative to a worldwide selection of populations. *Hum. Genet.* **116**, 105-113 (2005).
162. Johansson, A., Vavruch-Nilsson, V., Cox, D. R., Frazer, K. A. & Gyllensten, U. Evaluation of the SNP tagging approach in an independent population sample--array-based SNP discovery in Sami. *Hum. Genet.* **122**, 141-150 (2007).
163. Portas, L. *et al*. History, geography and population structure influence the distribution and heritability of blood and anthropometric quantitative traits in nine Sardinian genetic isolates. *Genet. Res. (Camb)* **92**, 199-208 (2010).
164. Biino, G. *et al*. Genetic architecture of hand quantitative ultrasound measures: a population-based study in a Sardinian genetic isolate. *Bone* **46**, 1197-1203 (2010).
165. Pistis, G. *et al*. High differentiation among eight villages in a secluded area of Sardinia revealed by genome-wide high density SNPs analysis. *PLoS One* **4**, e4654 (2009).
166. McQuillan, R. *et al*. Runs of homozygosity in European populations. *Am. J. Hum. Genet.* **83**, 359-372 (2008).
167. Krawczak, M. *et al*. PopGen: population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships. *Community Genet.* **9**, 55-61 (2006).
168. Hillege, H. L. *et al*. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* **106**, 1777-1782 (2002).
169. Shepherd, J. *et al*. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am. J. Cardiol.* **84**, 1192-1197 (1999).
170. Shepherd, J. *et al*. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* **360**, 1623-1630 (2002).
171. Ford, I. *et al*. Reduced glomerular filtration rate and its association with clinical outcome in older patients at risk of vascular events: secondary analysis. *PLoS Med.* **6**, e16 (2009).
172. Hofman, A., Grobbee, D. E., de Jong, P. T. & van den Ouweland, F. A. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur. J. Epidemiol.* **7**, 403-422 (1991).
173. Hofman, A. *et al*. The Rotterdam Study: objectives and design update. *Eur. J. Epidemiol.* **22**, 819-829 (2007).
174. Hofman, A. *et al*. The Rotterdam Study: 2010 objectives and design update. *Eur. J. Epidemiol.* **24**, 553-572 (2009).
175. John, U. *et al*. Study of Health In Pomerania (SHIP): a health examination survey in an east German region: objectives and design. *Soz. Praventivmed.* **46**, 186-194 (2001).
176. Volzke, H. *et al*. Cohort profile: the study of health in Pomerania. *Int. J. Epidemiol.* **40**, 294-307 (2011).
177. Tonjes, A. *et al*. Genetic variation in GPR133 is associated with height: genome wide association study in the self-contained population of Sorbs. *Hum. Mol. Genet.* **18**, 4662-4668 (2009).
178. Tonjes, A. *et al*. Association of FTO variants with BMI and fat mass in the self-contained population of Sorbs in Germany. *Eur. J. Hum. Genet.* **18**, 104-110 (2010).
179. Veeramah, K. R. *et al*. Genetic variation in the Sorbs of eastern Germany in the context of broader European genetic diversity. *Eur. J. Hum. Genet.* **19**, 995-1001 (2011).
180. Ridker, P. M. *et al*. Rationale, design, and methodology of the Women's Genome Health Study: a genome-wide association study of more than 25,000 initially healthy american women. *Clin. Chem.* **54**, 249-255 (2008).
181. Guessous, I. *et al*. Caffeine intake and CYP1A2 variants associated with high caffeine intake protect non-smokers from hypertension. *Hum. Mol. Genet.* **21**, 3283-3292 (2012).
182. Guessous, I., Bochud, M., Theler, J. M., Gaspoz, J. M. & Pechere-Bertschi, A. 1999-2009 Trends in prevalence, unawareness, treatment and control of hypertension in Geneva, Switzerland. *PLoS One* **7**, e39877 (2012).
183. Weck, M. N., Stegmaier, C., Rothenbacher, D. & Brenner, H. Epidemiology of chronic atrophic gastritis: population-based study among 9444 older adults from Germany. *Aliment. Pharmacol. Ther.* **26**, 879-887 (2007).

184. Raum, E. *et al*. Changes of cardiovascular risk factors and their implications in subsequent birth cohorts of older adults in Germany: a life course approach. *Eur. J. Cardiovasc. Prev. Rehabil.* **14**, 809-814 (2007).
185. Schottker, B. *et al*. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. *Am. J. Clin. Nutr.* **97**, 782-793 (2013).
186. Boger, C. A. *et al*. Effect of ACE and AT-2 inhibitors on mortality and progression to microalbuminuria in a nested case-control study of diabetic nephropathy in diabetes mellitus type 2: results from the GENDIAN study. *Int. J. Clin. Pharmacol. Ther.* **44**, 364-374 (2006).
187. Boger, C. A. *et al*. Association of eGFR-Related Loci Identified by GWAS with Incident CKD and ESRD. *PLoS Genet.* **7**, e1002292 (2011).
188. Wild, P. S. *et al*. Distribution and categorization of left ventricular measurements in the general population: results from the population-based Gutenberg Heart Study. *Circ. Cardiovasc. Imaging* **3**, 604-613 (2010).
189. Wild, P. S. *et al*. A genome-wide association study identifies LIPA as a susceptibility gene for coronary artery disease. *Circ. Cardiovasc. Genet.* **4**, 403-412 (2011).
190. Lucae, S. *et al*. P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. *Hum. Mol. Genet.* **15**, 2438-2445 (2006).
191. Kloiber, S. *et al*. Variations in tryptophan hydroxylase 2 linked to decreased serotonergic activity are associated with elevated risk for metabolic syndrome in depression. *Mol. Psychiatry* **15**, 736-747 (2010).
192. Kohli, M. A. *et al*. The neuronal transporter gene SLC6A15 confers risk to major depression. *Neuron* **70**, 252-265 (2011).
193. Tayo, B. O. *et al*. Genetic background of patients from a university medical center in Manhattan: implications for personalized medicine. *PLoS One* **6**, e19166 (2011).
194. Winkelmann, B. R. *et al*. Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics* **2**, S1-73 (2001).
195. Heid, I. M. *et al*. Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. *Diabetes* **55**, 375-384 (2006).
196. Kollerits, B. *et al*. A common variant in the adiponutrin gene influences liver enzyme values. *J. Med. Genet.* **47**, 116-119 (2010).
197. Pruijm, M. *et al*. Heritability, determinants and reference values of renal length: a family-based population study. *Eur. Radiol.* **23**, 2899-2905 (2013).